BENZOTRIAZOLE MEDIATED HETEROALKYLATION AND ARYLALKYLATION IN ORGANIC SYNTHESIS

BY

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
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To my daughter, Stephanie, with love

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TABLE OF CONTENTS

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

α-(Benzotriazol-1-yl)alkyl groups are incorporated into amides, sulfides and electron-rich heteroaromatic systems. These benzotriazole derivatives undergo amidoalkylation, thioalkylation and heteroarylalkylation with the displacement of the benzotriazolyl group by varous nucleophiles to furnish a wide spectrum of useful organic compounds.

α-Amino isonitriles and α-alkylthio isonitriles are synthesized by the dehydrations of *N*-(α-aminoalkyl)formamides and *N*-[α-(alkylthio)alkyl]formamides, themselves prepared from the amidoalkylation of amines and thiols with 1-[(α-formylamino)alkyl]benzotriazoles.

α-(Benzotriazol-1-yl)alkyl phenyl sulfides, readily available from benzotriazole, an aldehyde and thiophenol, react smoothly with active aromatic compounds to afford a variety of thioalkylated products.

α-(Benzotriazol-1-yl)alkyl groups are incoporated into thiophene, furan and indole systems *via* the reaction of *N*-[(α-benzotriazol-1-yl)alkyl]carbamates, which are easily prepared from the condensation of benzotriazole, an aldehyde and a carbamate, with 2-methylthiophene, 2-methylfuran and 1-methylindole, respectively. Heteroarylalkylation of heteroaromatic compounds with these benzotriazole

derivatives provides a wide range of both symmetrical and unsymmetrical 1,1-bis(heteroaryl)alkanes.

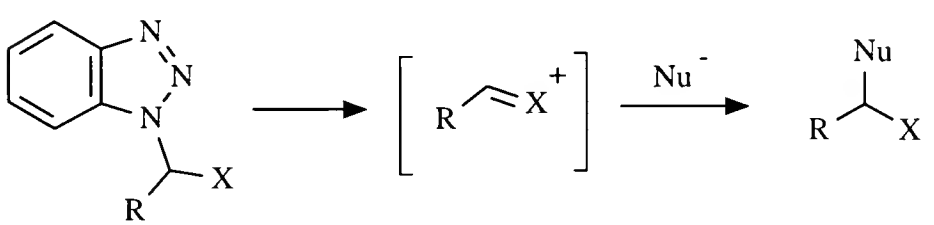
Following a similar protocol, a variety of 3-substituted indoles are prepared from the indolylalkylation of various nucleophiles with 1-methyl-3-[(α-benzotriazol-1-yl)alkyl]indole, which are obtained either *via* the condensation of 3-methylindole with *N*-[(α-benzotriazol-1-yl)alkyl]carbamates or *via* the reactions of lithiated 1-methyl-3-[(benzotriazol-1-yl)methyl]indole with electrophiles.

Indolylalkylation has been successfully extended to the synthesis of thieno[b]carbazoles, furo[b]carbazoles and indolo[b]carbazoles. Thus, 1-methyl-2-bromo-3-[(benzotriazol-1-yl)methyl]indole, available from the bromination of 1-methyl-3-[(benzotriazol-1-yl)methyl]indole, undergoes halogen-lithium exchange with *t*-butyllithium and the resulting carbanion reacts with thiophenecarboxaldehydes, furancarboxaldehydes and indolecarboxaldehyde. By subsequently quenching with methyl iodide, the corresponding methyl ether intermediate products are obtained in excellent yields. Intramolecular indolylalkylation of these intermediates is effected by refluxing in 1,2,4-trichlorobenzene or 1,2-dichlorobenzene, which is followed by simultaneous aromatization and thus provides these important novel polycyclic compounds.

CHAPTER I
GENERAL INTRODUCTION

Work in our laboratory has demonstrated benzotriazole as a useful synthetic auxiliary [91T2683]. One of the special features attributing to the usefulness of benzotriazole is its strong acidity ($pK_a \approx 8$) which endows it with two important properties. One is that it readily undergoes Mannich-type condensation with an aldehyde and a compound containing an active hydrogen atom to form a variety of benzotriazolyl derivatives, and the other is that its anion is a good leaving group which can be displaced by various types of nucleophiles in its derivatives of type Bt-C-heteroatom (N, S, or O) and Bt-C-Ar (Ar = electron rich aromatics). The combination of these two properties allows a wide spectrum of useful organic compounds to be readily accessible.

BENZOTRIAZOLE MEDIATED HETEROALKYLATION

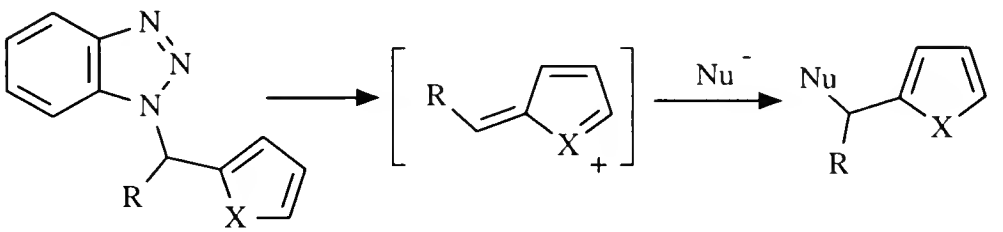


1.1 **1.2** X = N, S, O

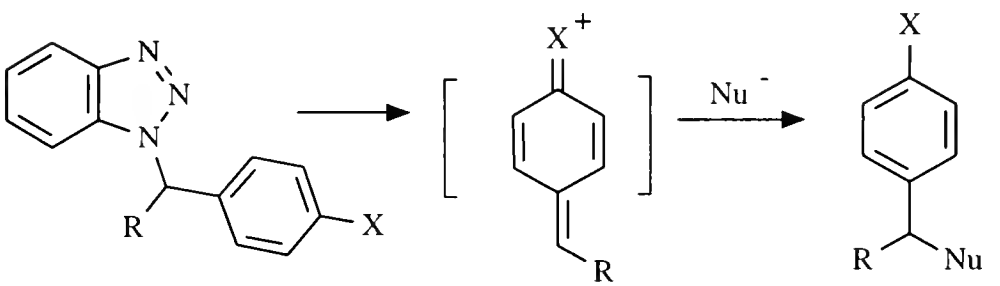
A conversion of a benzotriazolyl derivative Bt-C-heteroatom **1.1** with displacement of benzotriazole by nucleophiles is called *heteroalkylation mediated by benzotriazole*. Conceptually similar, *benzotriazole mediated arylalkylation* indicates

the displacement of type Bt-C-Ar **1.3** and **1.5** by nucleophiles. In these processes, the dissociation of the C-Bt bond is assisted by the lone electron pair on the heteroatom X to form reactive intermediates, cations **1.2**, **1.4** and **1.6** [87JCS(P1)2673, 89H1121], which subsequently react with nucleophiles to fulfil the transformations.

BENZOTRIAZOLE MEDIATED ARYLALKYLATION



1.3 **1.4** X = N, S, O



1.5 **1.6** X = N, O

X at *para* or *ortho* position

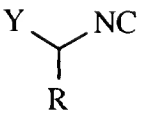
Since benzotriazolyl derivatives are usually more stable and/or more readily accessible than their chloro or bromo analogues, the benzotriazole-mediated methodology proves to be a highly advantageous one and in many cases even a necessity.

The objective of this project is to investigate the applications of benzotriazole mediated heteroalkylation and arylalkylation in the synthesis of a variety of useful organic compounds, and the results will be reported in five chapters. Chapter II describes the synthesis of α-amino isocyanides and α-alkylthio isocyanides *via* the amidoalkylation of amines and thiols with 1-(1-formylaminoalkyl)benzotriazole, followed by the dehydration of formed intermediate products. Chapter III discusses the thioalkylation of reactive aromatic compounds with α-(benzotriazol-1-yl)benzyl phenyl sulfide. Chapters IV and V deal with the synthetic applications of benzotriazole mediated heteroarylalkylation in the synthesis of 1,1-bis(heteroaryl)-alkanes and 3-substituted indoles. The work in Chapter VI extends the benzotriazole mediated heteroarylalkylation to the synthesis of thieno[b]carbazoles, furo[b]-carbazoles and indolo[b]carbazoles.

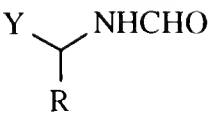
CHAPTER II
AMIDOALKYLATION OF AMINES AND THIOLS WITH 1-(1-FORMYLAMINOALKYL)BENZOTRIAZOLE: SYNTHESIS OF α-AMINO ISONITRILES AND α-ALKYLTHIO ISONITRILES

2.1 Introduction

The chemistry of isonitriles in general is well documented [71MI1], but far less work has been reported on functionalized, specifically α-substituted isonitriles **2.1**. Bohme and Fuchs reported the three-step synthesis of (isocyanomethyl)phenyl sulfone (**2.1**, Y = $PhSO_2$, R = H) and of *N*-(isocyanomethyl)phthalimide starting from the corresponding (formamidomethyl)dialkylamine, but they failed to obtain (alkylthio)methyl isocyanides (**2.1**, Y = RS) [70CB2775]. Diethyl isocyanomethylphosphonate (**2.1**, Y = $(EtO)_2P(O)$, R = H) was prepared from the reaction of triethyl phosphite and an *N*-(formylaminomethyl)trimethylammonium salt followed by treatment with $POCl_3$ in the presence of triethylamine [73TL633]. Other isocyanomethyl substituted phosphorus compounds have also been reported [74LA44, 81LA99, 81LA709]. Treatment of $O_2NNPrCH_2Cl$ with NaCN-$ZnCl_2$ gave *N*-(isocyanomethyl)-*N*-nitropropylamine (**2.1**, Y = O_2NNPr, R = H) which rearranged to its corresponding nitrile form [81AP459]. 1-Isocyanomethylazoles RCH_2NC (R = 1-imidazolyl, 1,2,4-triazol-2-yl, 1-benzimidazolyl and benzotriazolyl) were synthesized by the reaction of RH with $HCONHCH_2N^+Me_3I^-$ followed by dehydration of RCH_2NHCHO using $POCl_3$ or PPh_3/CCl_4 [83CPB723]. Preparations of a few α-(arylthio)methyl isonitriles (**2.1**, Y = ArS, R = H) [88TL1435] and 1-(arylthio)-



2.1



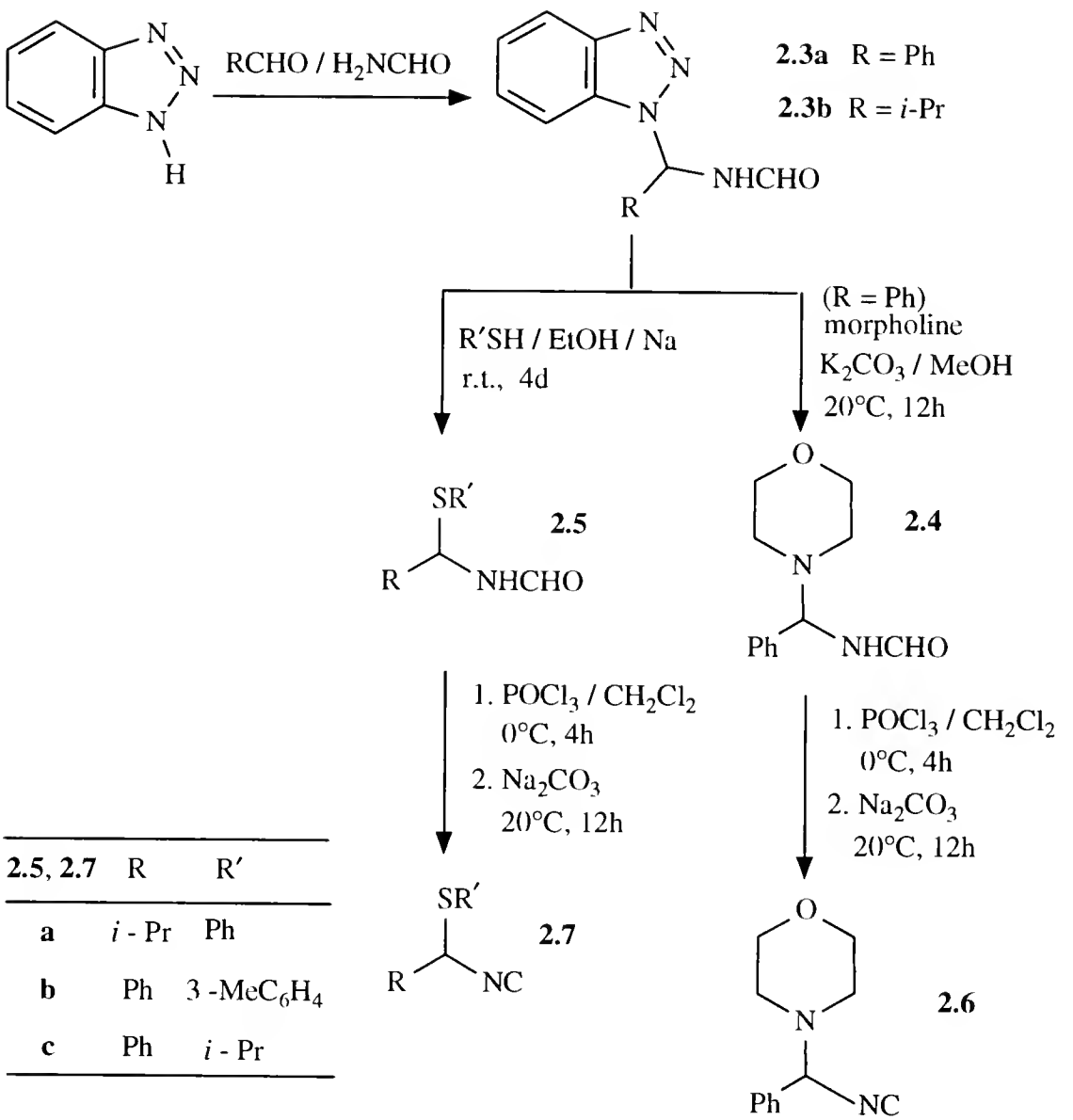
2.2

alkenyl isonitriles [85RTC177] have also been reported.

All these previously reported α-substituted isonitriles are isocyanomethyl derivatives (**2.1**, R = H). Our own group recently disclosed the synthesis of α-(benzotriazolyl)alkyl isonitriles (**2.1**, Y = benzotriazolyl, R = alkyl) by dehydration of 1-(1-formylaminoalkyl)benzotriazoles (**2.3**) which were prepared by the condensation of benzotriazole, an aldehyde and formamide [90JCS(P1)1847]. (Benzotriazol-1-yl)-alkyl isocyanides have been used as versatile synthons for the preparation of unsymmetrical formamidines. In this chapter, we now report for the first time the synthesis of an α-aminoisonitrile (**2.1**, Y = R_2N, R = alkyl) and of elaborated α-alkylthioisonitriles (**2.1**, Y = RS, R = alkyl) from 1-(1-formylaminoalkyl)-benzotriazoles.

2.2 Results and Discussion

α-Aminoisonitriles and α-alkylthioisonitriles were prepared as shown in Scheme 2.1. 1-[α-(Formylamino)benzyl]benzotriazole (**2.3a**) and 1-[1-(formylamino)--2-methylpropyl]benzotriazole (**2.3b**) were prepared from benzotriazole, formamide and the appropriate aldehyde as previously described [90JCS(P1)1847]. Reaction of benzotriazole derivative **2.3a** with morpholine in methanol at room temperature in the



2.5, 2.7	R	R′
a	*i* - Pr	Ph
b	Ph	3 -MeC_6H_4
c	Ph	*i* - Pr

Scheme 2.1

presence of potassium carbonate gave *N*-(α-morpholinobenzyl)formamide (**2.4**) in 62% yield. Compounds **2.3a** and **2.3b** reacted with sodium salts of three aromatic and aliphatic thiols in ethanol at room temperature to afford the desired *N*-[(alkylthio)-

alkyl]formamides **2.5a** - **2.5c** in good yields. The byproduct sodium or potassium benzotriazolate, produced during these reactions, was easily removed during the aqueous workup. Dehydration of the *N*-(α-aminoalkyl)- (**2.4**) and *N*-(α-alkylthio-alkyl)-formamides (**2.5a** - **2.5c**) with $POCl_3$ in the presence of *i*-Pr_2NH gave the corresponding α-aminoisonitrile **2.6** and α-alkylthioisonitriles **2.7a** - **2.7c** in good yields.

It is believed that the amidoalkylations of morpholine and thiols with compounds **2.3a** and **2.3b** involve electrophilic attack by the carbocation of type **1.2** (X = NHCHO) which is stabilized by the nitrogen atom as mentioned in the introduction.

The dehydration of formamide derivatives with $POCl_3$ in the presence of an amine and other dehydrating reagents, such as tosyl chloride [65CA11441], thionyl chloride and base [72JOC187] or triphenylphosphine in CCl_4 [71AG143] are well known. Therefore, the preparations of *N*-(α-aminoalkyl)- (**2.2**, Y = R_2N) and *N*-(α-alkylthioalkyl)-formamides (**2.2**, Y = RS) are the key to the synthesis of the corresponding α-substituted isonitriles **2.1**. (Formamidomethyl)dialkylamines have usually been synthesized by the condensation of formamide with formaldehyde and secondary amines, but the condensation is, in general, not applicable to either other aliphatic or aromatic aldehydes [70CB2775, 81CB3421]. Synthetic access to formamidomethyl alkyl sulfides (**2.2**, Y = RS, R = H), the precursors for (alkylthio)-methyl isonitriles, is available from the reactions of thiols with hydroxymethyl-formamide [85JCS(P1)75], *p*-tosylmethylformamide [87RTC159, 87T5073], quarternary ammonium cations [70CB2775, 88TL1435] and with chloromethyl-formamide [74AJC1579].

However, none of these methods has been used for the preparation of [α-(alkylthio)alkyl]formamides (**2.2**, Y = RS, R = alkyl). The novel aspect of our work is that using 1-(1-formylaminoalkyl)benzotriazoles now provides a convenient route to the preparation of both α-(formamidoalkyl)dialkylamines and α-(formamido-alkyl)alkyl sulfides in good yield. This method works particularly well with aromatic and aliphatic aldehydes under mild conditions.

N-(α-Morpholinobenzyl)formamide (**2.4**) and *N*-[(α-alkylthio)alkyl]-formamides (**2.5a-2.5c**) were characterized by elemental analyses and by their ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra of **2.4** and **2.5**, the NH protons appear as doublets at 8.64 to 9.15 ppm with coupling constants ranging from 9.3 - 10.0 Hz, and the formyl CH protons at 8.28-7.78 ppm with small coupling constants (0.9 Hz). In the ^{13}C NMR spectra, formyl carbonyl carbons appear at 160.0 - 161.2 ppm and CH carbons at 68.9 - 52.9 ppm. All of the α-substituted isocyanides are new compounds. The isocyanide structure is confirmed by the strong IR absortion band at 2250 cm^{-1} for the compound **2.6** and 2120 cm^{-1} for compounds **2.7**, and by the ^{13}C signals of the isocyanato carbons at 159.7 - 160.4 ppm. The structures of the isonitrile **2.6** is further confirmed by elemental analysis and of compounds **2.7a** - **2.7c** by high resolution mass spectra.

2.3 Experimental

Melting points were determined with a hot stage apparatus and were uncorrected. ^{1}H (300 MHZ) NMR and ^{13}C (75 MHz) NMR spectra were recorded on a Varian VXR spectrometer. High resolution mass spectra were obtained on a Finnigan Mat 95 spectrometer and IR spectra were measured on a Perkin-Elmer

Model 283B grating spectrometer. 1-[1-(Formylamino)benzyl]benzotriazole (**2.3a**) and 1-[1-(formylamino)-2-methylpropyl]benzotriazole (**2.3b**) were prepared as previously described [90JCS(P1)1847].

2.3.1 *N*-(α-Morpholinobenzyl)formamide (**2.4**)

A mixture of 1-(1-formylamidobenzyl)benzotriazole (**2.3**) (1.89 g, 7.5 mmol), morpholine (0.86 g, 10 mmol) and potassium carbonate (2.25 g) in methanol (20 ml) was stirred at 20°C overnight. The solvent was evaporated, the residue dissolved in ethyl acetate (100 ml), washed with aqueous sodium hydroxide (3 x 20 ml, 10%), water (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a white solid which was recrystallized from ethyl acetate/hexane (3/1) to give **2.4** as white needles (1 g, 62%), mp. 141-142°C. ^{1}H-NMR (DMSO-d_6): δ = 8.74 (d, 1H, J = 9.3 Hz, NH), 8.28 (d, 1H, J = 0.9 Hz, CHO), 7.47-7.30 (m, 5H, ArH), 5.71-5.68 (d, 1H, J = 9.6 Hz, CH), 3.57 (t, 4H, J = 4.2 Hz), 2.38 (t, 4H, J = 4.2 Hz); ^{13}C-NMR: δ = 161.2 (CO), 138.6, 128.3, 128.2, 127.6, 127.2, 68.9 (CH), 66.2 (CH_2O), 48.3 (CH_2N). Analysis for $C_{12}H_{16}N_2O_2$ (220.3): calc. C 65.43 H 7.32 N 12.72; found C 65.20 H 7.36 N 12.68.

2.3.2 *N*-(1-Phenylthio-2-methylpropyl)formamide (**2.5a**); Typical Procedure

A solution of thiophenol (3.3 g, 30 mmol) and sodium (0.72 g, 30 mmol) in absolute ethanol (60 ml) was added to a suspension of 1-(1-formylaminobenzyl)-benzotriazole (**2.3a**) (3.27 g, 15 mmol) in absolute ethanol (30 ml) with stirring at room temperature. The mixture was stirred for 4 days at room temperature. Ethanol

was removed under reduced pressure and the residue dissolved in ethyl acetate (100 ml), washed with aqueous NaOH (3 x 20 ml, 10%) and water (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent and recrystallization from ethyl acetate/hexane (3/1) gave **2.5a** as white needles (2.32 g, 74%), mp. 65-66°C. ^{1}H-NMR ($CDCl_3$): δ = 8.61 (d, 1H, J = 10.0 Hz, NH), 7.98 (d, 1H, J = 0.9 Hz, CHO), 7.44-7.25 (m, 5H, ArH), 5.31 (dd, 1H, J = 9.9, 5.4 Hz, CH), 1.98 (m, 1H, CH), 1.00 (m, 6H, 2 x CH_3); ^{13}C-NMR: δ = 160.4 (CO), 133.8, 131.1, 128.9, 126.9, 60.9, 33.1, 19.4, 18.2. Analysis for $C_{11}H_{15}NOS$ (209.2): calc. C 63.12 H 7.22 N 6.69; found C 62.99 H 7.33 N 6.66.

N-[α-(3-Methylphenylthio)benzyl]formamide (**2.5b**): White needles from AcOEt/hexane, 45%, mp 132-133°C. ^{1}H-NMR ($CDCl_3$): δ = 9.05 (d, 1H, J = 9.6 Hz, NH), 7.78 (s, 1H, CHO), 7.36-6.86 (m, 9H, ArH), 6.32 (d, 1H, J = 9.6 Hz, 1H), 2.04 (s, 3H, CH_3); ^{13}C-NMR: δ = 160.0 (CO), 138.9, 138.3, 133.2, 131.9, 128.8, 128.5, 128.4, 128.2, 128.1, 126.8, 56.8, 20.8. Analysis for $C_{15}H_{15}NOS$ (257.9): calc. C 70.1 H 5.88 N 5.44; found C 69.57 H 5.78 N 5.34.

N-[(α-Isopropylthio)benzyl]formamide (**2.5c**): Needles (AcOEt/hexane), 80%, mp. 62-63°C. ^{1}H-NMR (DMSO-d_6): δ = 9.15 (d, 1H, J = 9.6 Hz, NH), 8.13 (d, 1H, J = 0.6, CHO), 7.49-7.26 (m, 5H, ArH), 6.26 (d, 1H, J = 9.6 Hz, CH), 3.03 (m, 1H, CH), 1.32 (d, 3H, J = 6.6 Hz, CH_3); 1.19 (d, 3H, J = 6.6 Hz, CH_3); ^{13}C-NMR: δ = 160.1, 139.7, 128.4, 127.7, 126.6, 52.9, 34.6, 23.7, 22.5. Analysis for $C_{11}H_{15}NOS$ (209.2): calc. C 63.12 H 7.22 N 6.69; found C 63.34 H 7.19 N 6.65.

2.3.3 α-Morpholinobenzyl isocyanide (**2.6**); Typical Procedure for the Preparation of **2.6, 2.7a, 2.7b, 2.7c**

Diisopropylamine (0.303 g, 3 mmol) was added to *N*-(α-morpholinobenzyl)-formamide (**2.4**) (0.22 g, 1 mmol) in CH_2Cl_2 (40 ml). Phosphorous oxychloride (0.20 g, 1.3 mmol) in CH_2Cl_2 was added dropwise at 0°C with stirring. The solution was stirred for 4h at 0°C and aqueous sodium carbonate (8 ml, 20%) was added slowly. After stirring at 20°C for 1 h, CH_2Cl_2 (20 ml) and water (20 ml) were added. The organic layer was washed with water (3 x 15 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica, CH_2Cl_2) to give a yellowish solid (0.19 g, 96%), mp. 66-67°C. ^{1}H-NMR ($CDCl_3$): δ = 7.55-7.52 (m, 2H, ArH), 7.43-7.37 (m, 3H, ArH), 4.83 (s, 1H, CH), 3.74 (m, 4H, 2 x CH_2O), 2.60-2.57 (m, 4H, 2 x CH_2N); ^{13}C-NMR: δ = 132.3, 129.0, 128.8, 127.9, 115.1, 66.6, 62.3, 49.9; IR (KBr): ν = 2250.0 (-NC). Analysis for $C_{12}H_{14}N_2O$ (202.2): calc. C 71.26 H 6.96 N 13.85; found C 71.00 H 7.12 N 13.73.

1-Phenylthio-2-methylpropyl isocyanide (**2.7a**): This compound was prepared as an oil (81%) from **2.5a** by the same procedure as **2.6**. ^{1}H-NMR ($CDCl_3$): δ = 7.57-7.54 (m, 2H), 7.32-7.32 (m, 3H, ArH), 4.50 (d, 1H, J = 4.8 Hz, CH), 2.12 (m, 1H, CH), 1.13 (d, 3H, J = 5.1, CH_3), 1.11 (d, 3H, J = 5.1 Hz, CH_3); ^{13}C-NMR: δ = 158.8, 133.5, 131.5, 129.2, 128.8, 67.2, 32.9, 19.2, 17.5; IR (KBr): ν = 2120 (-NC). HRMS: $C_{11}H_{13}NS$, calc. 191.0752; found 191.0752.

α-(3-Methylphenylthio)benzyl isocyanide (**2.7b**): This compound was prepared as an oil (82%) from **2.5b** by the same procedure as **2.6**. ^{1}H-NMR ($CDCl_3$): δ = 7.40-7.22 (m, 9H, ArH), 5.81 (s, 1H, CH), 2.33 (s, 3H, CH_3); ^{13}C-NMR: δ =

160.4, 139.1, 135.4, 133.9, 131.8, 131.7, 131.6, 130.2, 129.1, 128.7, 126.3, 62.8 (CH), 21.1; IR (KBr): ν = 2120.1 cm^{-1} (-NC). HRMS: $C_{15}H_{13}NS$, calc. 239.0769; found 239.0769.

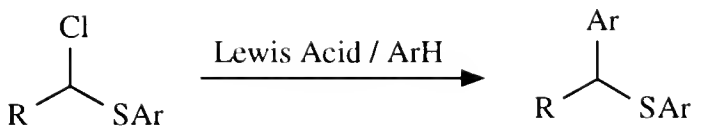
α-(Isopropylthio)benzyl isocyanide (**2.7c**): This compound was prepared as an oil (74%) from **2.5c** by the same procedure as **2.6**. ^{1}H-NMR ($CDCl_3$); δ = 7.49-7.34 (m, 5H, ArH), 5.74 (s, 1H, CH), 3.27 (m, 1H, CH), 1.43 (d, 3H, J = 6.6 Hz, CH_3), 1.29 (d, 3H, J = 6.6 Hz, CH_3); ^{13}C-NMR: δ = 159.7, 134.2, 128.9, 128.1, 125.1, 58.1, 36.3, 23.2, 22.1; IR (KBr): ν = 2120.1 (-NC). HRMS: $C_{11}H_{13}NS$, calc. 191.0772; found 191.0770.

CHAPTER III
THIOALKYLATION OF REACTIVE AROMATIC COMPOUNDS WITH α-(BENZOTRIAZOL-1-YL)BENZYL PHENYL SULFIDE

3.1 Introduction

The concept of "amidoalkylation", i.e. the replacement of an "active" hydrogen atom in OH, SH, NH or CH compounds by a group CRR"NHCOR′ is well recognized and has been reviewed [73S703, 70S49, 84S85, 84S181]. We have successfully employed benzotriazole mediated amidoalkylation in the synthesis of α-amino isocyanides and α-alkylthio isocyanides as discussed in Chapter II. However, the analogous concept of "thioalkylation", i.e. the replacement of H in XH by the group CRR"SR′ is less familiar, but has previously been accomplished in a variety of ways, using the following reagents actually or potentially of the type RR"CSR′Y where Y is a leaving group:

(a) Y = Halogen: Lewis acid-catalyzed dehalogenations of α-chloroalkyl phenyl sulfides (**3.1**) generate the corresponding carbocation which participates in electrophilic substitution of aromatic compounds to give the thioalkylation products **3.2** (Scheme 3.1). However, application of this method appears to be limited to cases where at least one of the alkyl groups in RR"C is strongly electron-withdrawing, i.e. structures **3.1** where R = CF_3 [89TL2265], CO_2Et, COR or CN [80TL2547, 91CPB1148]. α-Chloroalkyl alkyl sulfides (**3.1**) were prepared from the corresponding sulfides with *N*-chlorosuccinimide [77MI51].



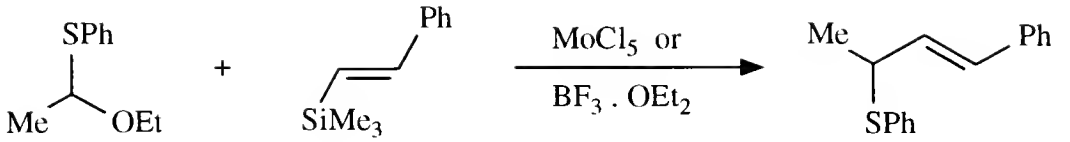
3.1 **3.2**

R = CF_3 , CO_2Et , COMe , COPh , CN

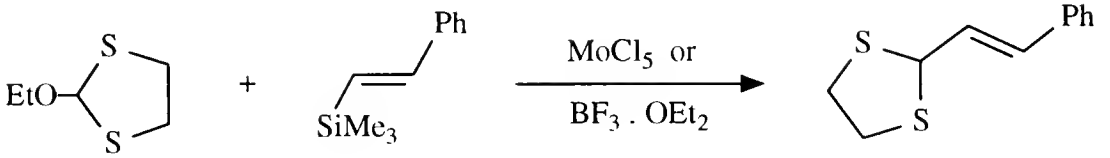
Scheme 3.1

(b) Y = OR: Treatment of trimethylstyrylsilanes with 1-ethoxy-1-(phenylthio)-ethane (**3.3**) or 2-ethoxy-1,3-dithiolane (**3.4**) in the presence of Lewis acids gives allyl sulfides **3.5** and **3.6**, respectively (Scheme 3.2) [83BCJ1569], but the yields were low (10 - 42%). The reaction of enol silyl ethers with 2-ethoxy-1,3-dithiolane (**3.4**) in the presence of zinc chloride affords half-protected 1,3-dicarbonyl compounds **3.7** (Scheme 3.2) [81TL3243]. However, these reactions were reported only for some unsaturated silicon compounds, not for thioalkylation of any aromatic or active methylene compound by RR"CSR′OEt. Lewis acid treatment of 2,2,2-trifluoro-1-methoxyethyl phenyl sulfide (**3.8**) does not generate the corresponding carbocation [87BCJ3823, 87JOC5489], and no thioalkylation was observed.

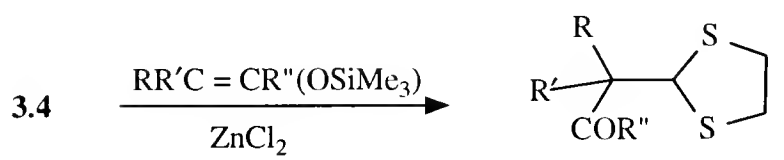
(c) Y = SR: Benzaldehyde diethylmercaptal (**3.12**), benzophenone diethyl-mercaptal and ethyl orthotrithioformate (**3.9**) react with copper(II) chelates **3.13** of 1,3-dicarbonyl compounds, or with anisole in the presence of cupric chloride, to give condensation or substitution products (**3.14** or **3.16**) [70BCJ2549]. However, the requirement for copper(II) salts for this thioalkylation has restricted its use. Moreover, in some cases olefinic compounds **3.15** are the major or only products as a result of the elimination of alkyl mercaptan from the condensation products [69JA4315]. In



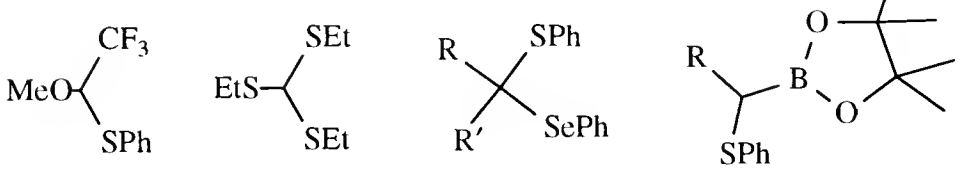
3.3 **3.5**



3.4 **3.6**

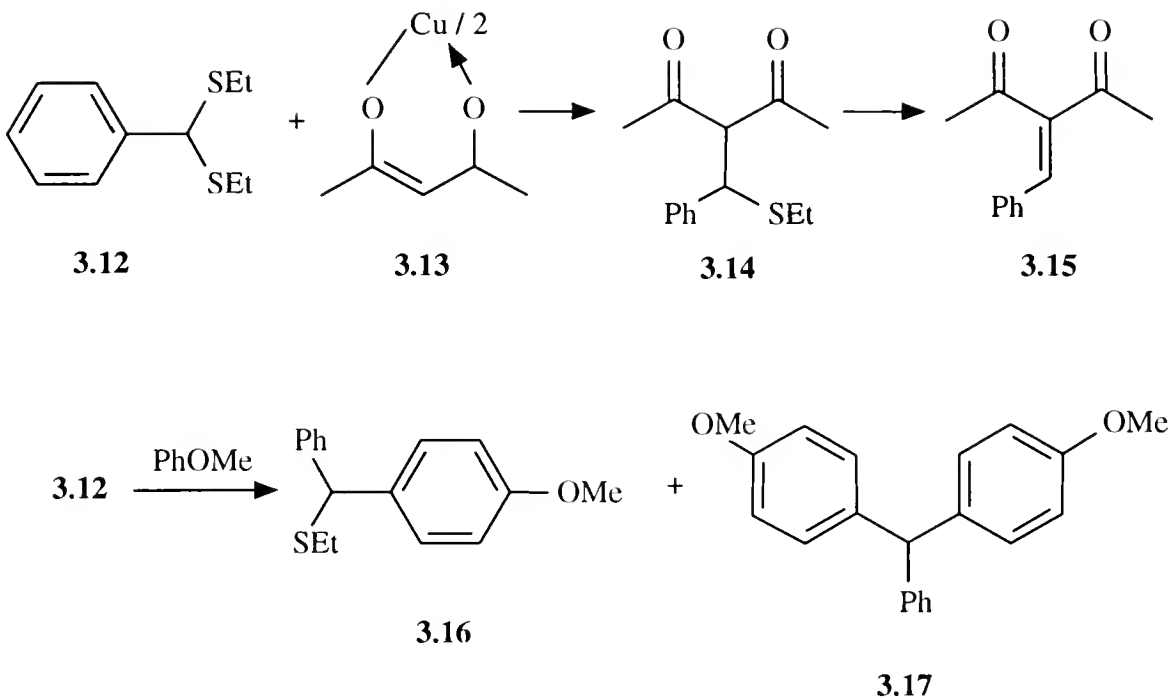


3.7



3.8 **3.9** **3.10** **3.11**

Scheme 3.2



Scheme 3.3

the case of anisole, the alkylthio group is often replaced by another anisole residue, thus forming a mixture of anisylphenylmethyl ethyl sulfide (**3.16**) and dianisylphenylmethane (**3.17**) (Scheme 3.3). Ethyl orthotrithioformate (**3.9**) yields three products [69JA4315].

(d) Y = SeR: The sulfo-selenoacetals **3.10** are cleaved by butyllithium in THF (-78°C) to give α-sulfo-carbanions, which add to a variety of carbonyl compounds and enolisable ketones, producing the β-hydroxysulfides [75TL1617]. But the preparation of the sulfo-selenoacetals **3.10** generally required treatment of selenoacetals with butyllithium followed by thiolation [75TL1613].

Carbanions from deprotonation of α-(phenylthio)alkaneboronic esters **3.11** can be acylated with methyl esters to form α-(phenylthio)ketones [78JA1325]. However, the deprotonation of a boronic ester requires lithium diisopropylamide and the phenylthioalkylboronic esters themselves have to be made from (phenylthio)alkyl-lithiums.

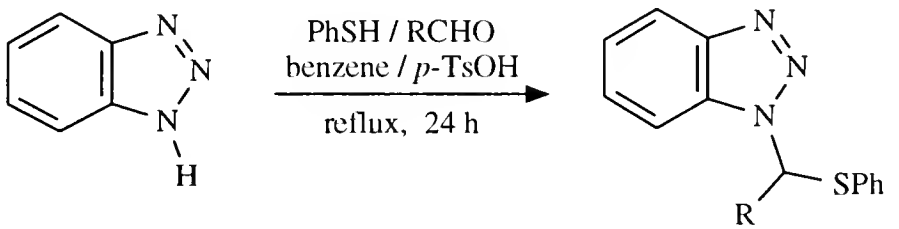
Acid catalyzed reactions of phenols with dicyclohexylcarbodiimide and dimethyl sulfoxide can be used for the (methylthio)methylation of phenols but gives low yields (3 - 38%) [66JA5855].

We now report in this chapter our results on the reaction of α-(benzotriazol-1-yl)alkyl phenyl sulfides, a new useful thioalkylation reagent, with various electron-rich aromatic compounds.

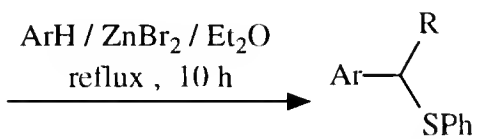
3.2 Results and Discussion

Thioalkylation reagents, α-(benzotriazol-1-yl)benzyl phenyl sulfide (**3.18a**) and [α-(benzotriazol-1-yl)-α-(4-methylphenyl)]methyl phenyl sulfide (**3.18b**) were prepared from thiophenol, an aldehyde and benzotriazole in good yields [91HCA1931]. The thioalkylation reactions were carried out in dry ether at reflux in the presence of equimolar amounts of zinc bromide under argon. Thus, the α-(benzotriazolyl)alkyl phenyl sulfides **3.18a** and **3.18b** reacted with a variety of active aromatic compounds to give the desired thioalkylation products **3.19a-i** in moderate to good yields. These reactions and results are listed in Scheme 3.4 and Table 3.1. The active aromatic compounds used include anisole, dimethoxybenzene and methoxynaphthalenes, phenols and naphthols. However, di- or trialkyl substituted benzenes are not reactive enough to undergo the thioalkylation, and for

N,N-dimethylaniline no sulfur containing product was isolated but a product similar to leucomalachite green was obtained. Presumably the phenylthio group was also replaced by *N,N*-dimethylaniline. Similar reactions have been reported [69JA4315].



3.18a R = Ph 47 %
b R = 4 - MeC_6H_4 64 %



3.19

3.19	R	Ar	**3.19**	R	Ar
a	Ph	4-$MeOC_6H_4$	**f**	Ph	4-HOC_6H_4
b	Ph	4-$MeOC_{10}H_6$	**g**	Ph	2-Me-4-HOC_6H_3
c	Ph	1-$MeOC_{10}H_6$	**h**	Ph	4-$HOC_{10}H_6$
d	Ph	2-$MeOC_{10}H_6$	**i**	4-MeC_6H_4	3,4-$(MeO)_2C_6H_3$
e	Ph	3,4-$(MeO)_2C_6H_3$			

Scheme 3.4

By analogy with the amidoalkylation discussed in Chapter II, the thioalkylation of aromatics with compounds **3.18a** and **3.18b** presumably goes through the carbocation of type **1.2** (X = SPh). The presence of $ZnCl_2$ is essential in

these reactions since the coordination of lone pair electrons on the nitrogen of benzotriazolyl group with $ZnCl_2$ greatly enhances its leaving ability, thus facilitating the reactions.

For monosubstituted benzenes (anisole and phenol) the thioalkylation occurred at the *para*-position as clearly shown by the typical signals for the *para* disubstituted benzene in the ^1H NMR spectra of the thioalkylation products (**3.19a** and **3.19f**). The thioalkylation of 2-substituted naphthalenes occured at the 1-position as we compared the ^1H NMR spectrum of the isolated product (**3.19d**) with that of the starting material. However, 1-methoxynaphthalene reacted to give mainly the 4-substituted product (**3.19b**) and a small amount of the 2-substituted isomer (**3.19c**). These isomers were separated by column chromatography and assigned by their ^1H NMR spectra. For the 4-substituted product **3.19b**, the doublet of C4 proton at 7.60 ppm [88MI1] disappeared and the doublet of C2 proton at 6.50 remained. By contrast, the C4 proton was seen and C2 proton was replaced in the ^1H NMR of the compound **3.19c**.

The thioalkylation products are all new except for **3.19a** [68CA39258, 67MI105]. The structures were characterized by their elemental analyses or high resolution mass spectra (Table 3.2) and by their ^1H and ^{13}C NMR spectral data. The ^1H and ^{13}C NMR chemical shifts and their assignments are listed in the experimental section. In the ^1H NMR spectra, typical singlets were observed at 5.38-6.72 ppm for the CH group. Generally, the CH protons of the three 1-hydroxy- or 1-methoxynaphthalenes (**3.19b, 3.19c** and **3.19g**) appeared at relatively downfield (6.23 - 6.72 ppm), while those of other thioalkylation products occured at higher field (5.38 - 5.63 ppm). In the ^{13}C NMR spectrum the CH carbon appeared at 48.7 - 60.4 ppm.

In conclusion, hydroxy or methoxy substituted benzenes and naphthalenes react under mild conditions with α-(benzotriazol-1-yl)alkyl phenyl sulfides (themselves easily available from benzotriazole, an aldehyde and thiophenol) to form the thioalkylation products. Although the yields are moderate, the products are easily purified. The use of our benzotriazole methodology in comparison to other thioalkylation reagents is advantageous in that our method gives similar yields under significantly milder conditions. Moreover, the reagents of the type α-(benzotriazol-1-yl)benzyl phenyl sulfide offer advantages over the previous reagents in being more easily prepared and/or more stable.

3.3 Experimental

Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were recorded on a Varian VXR spectrometer in $CDCl_3$ with TMS as the internal standard. Mass spectra were obtained from a Finnigan Mat 95. Column chromatography was performed with MCB silica gel (230-400 mesh).

3.3.1 α-(Benzotriazol-1-yl)benzyl phenyl sulfide (**3.18a**); Typical procedure

A mixture of benzotriazole (3.6 g, 30 mmol), thiophenol (3.3 g, 30 mmol) and benzaldehyde (3.2 g, 30 mmol) was refluxed in benzene (200 mL) in the presence of *p*-toluenesulfonic acid (0.5 g) under a Dean-Stark head. After the collection of water in the trap ceased (24 h), the reaction mixture was poured into aqueous sodium hydroxide solution (500 mL, 5%) and shaken well to remove unreacted benzotriazole

and thiol. Diethyl ether (300 ml) was added to the mixture and the organic layer separated, washed with water, dried ($MgSO_4$) and the solvent removed to give an oily residue which was recrystallized from Et_2O, 4.4 g (47%), mp. 80 - 82°C (Lit. [91HCA1931] mp. 80 - 81°C).

[(benzotriazol-1-yl)(4-methylphenyl)]methyl phenyl sulfide (**3.18b**): Yield 64%, mp. 97-98°C; ^{1}H NMR($CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.57 (m, 3H), 7.40 (t, J= 7.5 Hz, 1H), 7.35-7.10 (m, 8H), 2.29 (3H, CH_3); ^{13}C NMR δ 138.7, 133.2, 132.1, 130.6, 129.4, 129.1, 128.9, 128.4, 127.7, 127.6, 127.2, 124.3, 119.4, 111.3, 66.9, 20.7 (CH_3). Analysis for $C_{20}H_{17}N_3S$ (331.4): calc. C 72.48 H 5.17 N 12.68; found C 72.14 H 5.05 N 12.27.

3.3.2 1-(4-Methoxyphenyl)-1-phenyl-1-phenylthiomethane (**3.19a**); Typical procedure for thioalkylation

Anisole (0.54 g, 5 mmol) in dry ether (20 mL) was added to a solution of α-(benzotriazol-1-yl)benzyl phenyl sulfide (**3.18a**, 1.59 g, 5 mmol) and zinc bromide (1.4 g, 5 mmol) in dry ether (50 mL). The mixture was refluxed under argon for 10 hr, cooled, filtered and the solvent removed under reduced pressure. The oily residue was chromatographed with hexane-chloroform (2:1) as eluent and recrystallized from ether-petroleum ether to give colorless prisms. ^{1}H NMR δ 7.40 (d, J = 7.5 Hz, 2H), 7.35-7.13 (m, 10H), 6.80 (d, J = 7.5 Hz, 2H), 5.51 (s, 1H), 3.72 (s, 3H); ^{13}C NMR δ 158.6, 141.2, 136.6, 133.0, 130.3, 129.4, 128.6, 128.5, 127.1, 126.4, 113.8, 56.7, 55.1.

Other thioalkylation products were prepared similarly from the appropriate aromatics and compounds **3.18a** or **3.18b**.

1-(4-Methoxy-1-naphthyl)-1-phenyl-1-(phenylthio)meth ane(**3.19b**): ^{1}H NMR δ 8.30 (d, J = 9.4 Hz, 1H), 8.04 (d, J = 9.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (m,

2H), 7.30 (m, 1H), 7.29-7.04 (m, 9H), 6.73 (d, J = 8.1 Hz, 1H), 6.24 (s, 1H, CH), 3.87 (s, 3H); ^{13}C NMR δ 155.1, 132.4, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 126.8, 126.6, 126.9, 124.9, 124.0, 123.3, 122.7, 103.2, 55.4, 53.1.

1-(1-Methoxy-2-naphthyl)-phenyl-1-(phenylthio)methane (**3.19c**): ^{1}H NMR δ 8.31 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.45-7.32 (m, 2H), 7.30-7.12 (m, 3H), 6.77 (d, J = 8.1 Hz, 1H), 6.72 (s, 1H, CH), 6.59 (d, J = 8.1 Hz, 1H), 3.91 (s, 3H, OCH_3); ^{13}C NMR δ 154.4, 144.0, 132.6, 131.9, 129.8, 128.4, 127.7, 126.6, 126.5, 126.3, 126.0, 124.8, 124.0, 122.5, 103.0, 55.3, 48.7.

1-(2-Methoxy-1-naphthyl)-1-phenyl-1-phenylthiomethane (**3.19d**): ^{1}H NMR δ 7.67 (m, 3H), 7.39-7.26 (m, 5H), 7.24-7.06 (m, 8H), 5.42 (s, 1H), 3.79 (s, 3H); ^{13}C NMR δ 157.6, 139.6, 134.4, 132.4, 129.2, 128.7, 128.6, 128.5, 127.8, 127.7, 127.6, 127.5, 127.4, 126.6, 126.2, 123.4, 118.5, 105.8, 60.4, 55.0.

4-[Phenyl(phenylthio)methyl]-1,2-dimethoxybenzene (**3.19e**): ^{1}H NMR δ 7.31 (d, J = 7.8 Hz, 2H), 7.20-7.00 (m, 8H), 6.85 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 5.41 (s, 1H, CH), 3.69 (s, 3H), 3.68 (s, 3H); ^{13}C NMR δ 148.7, 148.0, 140.9, 136.0, 133.3, 130.3, 128.6, 128.4, 128.1, 127.1, 126.4, 120.5, 111.4, 110.8, 56.9, 56.8, 55.6.

4-[Phenyl(phenylthio)methyl]phenol (**3.19f**): ^{1}H NMR δ 7.40 (d, J = 8.6 Hz, 2H), 7.30-7.10 (m, 9H), 6.82 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.5 Hz, 2H), 5.49 (s, 1H, CH), 5.37 (br, 1H, OH); ^{13}C NMR δ 154.6, 141.1, 136.1, 133.4, 130.4, 129.7, 128.5, 128.3, 127.1, 126.5, 120.7, 115.3, 56.7.

3-Methyl-4-[phenyl(phenylthio)methyl]phenol (**3.19g**): ^{1}H NMR δ 7.40-7.36 (m, 3H), 7.28-7.10 (m, 8H), 6.63 (m, 2H), 5.65 (s, 1H, CH), 5.30 (br, 1H, OH), 2.27 (s, 3H, CH_3); ^{13}C NMR δ 154.5, 140.6, 137.6, 136.7, 131.1, 130.0, 129.8, 128.7, 128.6, 128.4, 127.0, 126.3, 117.3, 113.0, 53.3 (CH), 19.6 (CH_3).

4-[Phenyl(phenylthio)methyl]-1-naphthol (**3.19h**): ^{1}H NMR δ 8.21 (d, 1H), 8.05 (d, 1H), 7.54 (d, 1H), 7.40 (m, 3H), 7.35-7.02 (m, 9H), 6.62 (d, 1H), 6.23 (s, 1H, CH), 5.94 (br, 1H, OH); ^{13}C NMR δ 151.3, 140.8, 137.0, 132.1, 129.2, 128.8, 128.7, 128.6, 128.5, 127.9, 127.1, 127.0, 126.8, 126.1, 124.9, 123.4, 122.5, 107.9, 53.2 (CH).

4-[(4-Methylphenyl)(phenylthio)methyl]-1,2-dimethoxy benzene (**3.19i**): ^{1}H NMR δ 7.20 (d, J = 7.6 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.05-6.95 (m, 5H), 6.86 (s, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.38 (s, 1H, CH), 3.66 (s, 6H, 2 x OCH_3), 2.16 (s, 3H, CH_3); ^{13}C NMR: δ 148.7, 147.9, 137.9, 136.7, 136.3, 133.5, 130.1, 129.1, 128.5, 128.0, 126.2, 120.4, 111.4, 110.8, 56.6, 55.7, 55.6, 20.9 (CH_3).

Table 3.1 Thioalkylation of Active Aromatic Compounds

Prod-uct	ArH	Thio-alkylation position	Yield (%)	mp (°C)
3.19a	PhOMe	4	50	96-98
3.19b	1-$MeOC_{10}H_7$	4	56	119-121
3.19c	1-$MeOC_{10}H_7$	2	9	116-117
3.19d	2-$MeOC_{10}H_7$	1	30	123-125
3.19e	*o*-$(MeO)_2C_6H_4$	4	51	92-93
3.19f	PhOH	4	40	99-100
3.19g	*m*-MeC_6H_4OH	4	52	oil
3.19h	1-$C_{10}H_7OH$	4	41	oil
3.19i	*o*-$(MeO)_2C_6H_4$	4	40	oil

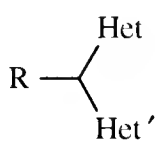
Table 3.2 Microanalyses / HRMS data of Thioalkylated Products **3.19a-i**

Compd	Molecular Formula	Analysis / HRMS			
		C	H	C	H
		required		found	
3.19a	$C_{20}H_{18}OS$	78.40	5.92	78.31	5.90
3.19b	$C_{24}H_{20}OS$	80.86	5.66	80.62	5.63
3.19c	$C_{24}H_{20}OS$	80.86	5.66	80.94	5.63
3.19d	$C_{24}H_{20}OS$	80.86	5.66	81.27	5.72
3.19e	$C_{21}H_{20}OS$	74.97	5.99	74.90	5.97
3.19f	$C_{19}H_{16}OS$	78.05	5.22	77.65	5.45
3.19g	$C_{20}H_{18}OS$	306.1087		306.1087	
3.19h	$C_{23}H_{18}OS$	343.1157		343.1171	
3.19i	$C_{22}H_{22}OS$	350.3333		350.1333	

CHAPTER IV
HETEROARYLALKYLATION OF HETEROAROMATIC COMPOUNDS: CONVENIENT NOVEL SYNTHESES OF 1,1-BIS(HETEROARYL)ALKANES

4.1 Introduction

Bis-heterocyclylmethanes are of interest to the food industry as they are present as natural compounds in food and beverage items such as licorice [77MI1238]. For example, difuryl- and dithienyl- alkanes are flavor agents in coffee [90MI802, 67HCA628]. Many bisheterocyclylmethanes are also of importance in dyestuff chemistry as they are readily oxidized to the corresponding cyanine dyes [63MI540, 63CA573861a]. Furthermore, 1,1-bis(heterocyclyl)alkanes are important intermediates in the synthesis of various heterocyclic macromolecules [77MI47, 78CA90046p], for example dipyrromethanes have been widely used as synthetic intermediates in total syntheses of porphyrins [78MI1]. The action of dichloromethyl alkyl ether and tin(IV) chloride on diheteroarylmethanes is a useful route to polycyclic heteroaromatic systems [73JCS(P1)1099].



4.1

Several synthetic routes to bis-heteroarylmethanes **4.1** are known, but none is both general and convenient. Many are only applicable to the preparation of

symmetrical bis(heterocyclyl)methanes. Di-2-furylmethane has been prepared by the reduction of di-2-furyl ketone [32HCA1066] and also by the interaction of 2-chloromercurifuran and furfuryl chloride [33JA3302]. Reduction of the corresponding diheteroarylmethanols also gives diheteroarylmethanes [73JCS(P1)1099]. However, most of these methods are limited to the preparation of compounds in which an unsubstituted methylene group links the two heteroaromatic rings (**4.1**, Het = Het′, R = H), and their utility is further restricted by the inaccessibility of suitable diheteroaryl ketones and methanols. The reaction of a heteroaryl-lithium with a heteroarylmethyl chloride [73JCS(P1)1099] gives a diheteroaryl methane, but it requires severe conditions. Thiophenes, furans and pyrroles with free α-positions are susceptible to electrophilic attack by aldehydes or ketones and this is a well known route to (diheteroaryl)methane derivatives [63AHC1]. However, this type of condensation generally requires a strong inorganic acid catalyst, such as 75% H_2SO_4 [51JA1377] or hydrochloric acid [56CJC1147]. These experimental conditions present the drawback of causing resinification [51JA1270] and degradation [72ACS1018] of the heterocyclic rings of substrates and products. An improvement of this condensation using macroporous ion-exchange resins as catalyst [89SC3169] is satisfactory for the preparation of difuryl and dithienyl derivatives.

Unsymmetrical bis(heterocyclyl)methanes are far less explored, in fact some structurally simple bis(heterocyclyl)methanes, especially with two different heterocyclic ring systems, are not known. The few synthetic procedures available have only led to a limited number of compounds of this class. Perhaps the most important is the reduction of the corresponding alcohols. Sodium borohydride-trifluoroacetic acid reduction of diheteroarylmethanols gives

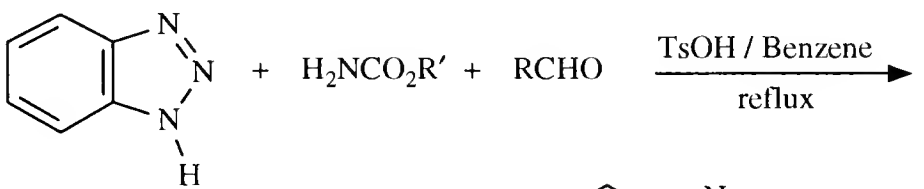
diheteroarylmethanes in 32-76% yield [91OPP403], however, use of this reduction method has been confined to the methylene derivatives (**4.1**, R = H). Moreover, the preparation of diheteroarylmethanols usually requires lithiation under severe conditions. Alkyl α-methoxy- and α-hydroxy-pyrrylacetates interact with *N*-methylindole in the presence of Lewis acids to give diarylacetic esters [92SL745], but the starting materials are not easily available and this method is not general. Condensation of an α-acetoxymethylpyrrole with an appropriately substituted pyrrole with a free α-position in acetic acid [70AJC2443], in the presence of toluene *p*-sulphonic acid [72TL2203] or Montmorillonite clay [85TL793] produces unsymmetrical dipyrrolylmethanes. However, the isolation of the product from tarry reaction by products is tedious. Symmetrical pyrrolylmethanes are often formed as by-products by self-condensation of the acetoxymethylpyrrole [74JCS(P1)1188, 75CC570], and the method is useful only for the fully substituted dipyrrolylmethanes in order to avoid polymerization. Unsymmetrical difurylmethanes are obtained from the reaction of 5-methylfurylphosphinyl carbinol and furan followed by a Wittig-Horner reaction [85TL6399], but this method is not general. Alkylation of furan, thiophene, and pyrrole with furfuryl alcohol in the presence of the strongly acidic Amberlyst 15 cation-exchange resin affords the respective 2-furylhetarylmethanes [89KGS746], however, the yields are low and purification is difficult (preparative GLC) because of the formation of difurylmethyl ether and resinous by-products.

We now report in this chapter a general and convenient method for the preparation of both symmetrical and unsymmetrical bis-heterocyclic alkanes *via* the heteroarylalkylation of heteroaromatic compounds with α-benzotriazolylalkyl substituted furans, thiophenes and indoles.

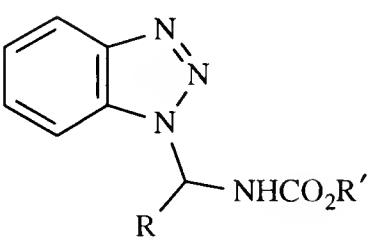
4.2 Results and Discussion

4.2.1 Condensation of Benzotriazole, Aldehydes and Carbamates

The Mannich condensation of benzotriazole, an aldehyde, and a carbamate is known to give *N*-(1-benzotriazol-1-ylalkyl)carbamate in good yield [90JOC2206]. Thus the benzotriazole derivatives **4.2a**, **4.2b**, **4.2c** and **4.2d** were prepared by the literature procedures in 84%, 78%, 74% and 69% yields respectively (see Table 4.1) (Scheme 4.1). The ^{1}H and ^{13}C NMR spectra of these benzotriazolylalkyl carbamates (Table 4.2 and 4.3) indicated that they were all benzotriazol-1-yl isomers, furthermore no isomerization to the 2-isomer was observed in dimethyl sulfoxide at room temperature. This behaviour is similar to that found for *N*-(1-amidoalkyl)benzotriazoles [90JOC2206].



4.2a: R = *i*-Pr , R′ = Me 84 %
4.2b: R = Ph , R′= Me 78 %
4.2c: R = H , R′ = Me 74 %
4.2d: R = R′= Ph 69 %

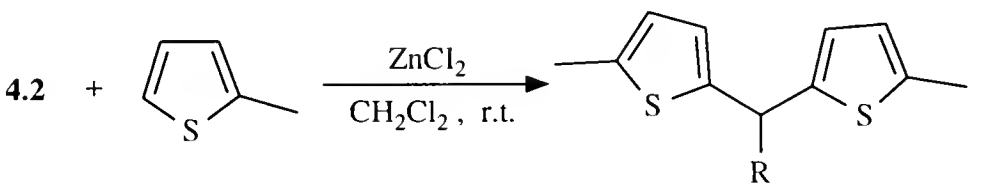


4.2

Scheme 4.1

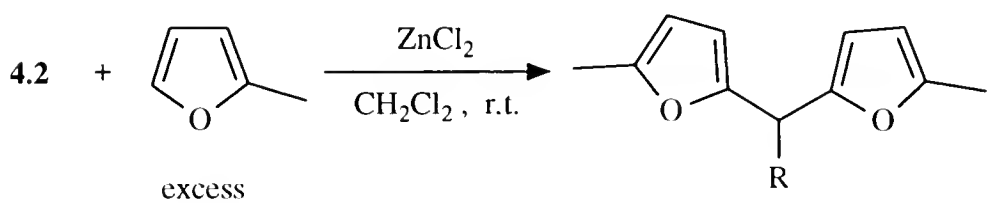
4.2.2 Preparation of Symmetrical Bis-heteroarylalkanes

The methyl *N*-(α-benzotriazol-1-ylalkyl)carbamates **4.2a**, **4.2b** and **4.2c** reacted smoothly with an excess amount of 2-methylthiophene or 2-methylfuran in CH_2Cl_2 in the presence of zinc chloride at room temperature to give the corresponding symmetrical 1,1-bis(heteroaryl)alkanes. In this reaction, both



4.3

4.3a: R = *i*-Pr 90 %
4.3b: R = Ph 94 %
4.3c: R = H 86 %



4.4

4.4a: R = *i*-Pr 88 %
4.4b: R = Ph 90 %

Scheme 4.2

benzotriazole and methoxycarbamoyl acted as leaving groups and each was replaced by a heterocycle. 1,1-Di(5-methylthiophen-2-yl)alkanes **4.3a**, **4.3b** and **4.3c** and 1,1-di-(5-methylfur-2-yl)alkanes **4.4a** and **4.4b** were thus prepared in excellent yields (86 - 94%) (Table 4.4) as shown in Scheme 4.2. As expected, the substitution

occurred at the free α-positions of furan and thiophene as shown by the ^1H NMR spectra of the products.

Similarly, phenyl *N*-(α-benzotriazol-1-ylbenzyl)carbamate **4.2d** also gave α,α-di(5-methylfur-2-yl)toluene **4.4b** in 65% yield on treatment with an excess of 2-methylfuran in CH_2Cl_2 with zinc bromide as the catalyst. However, the methyl carbamate is a better reagent in light of the yield and the ease of product purification.

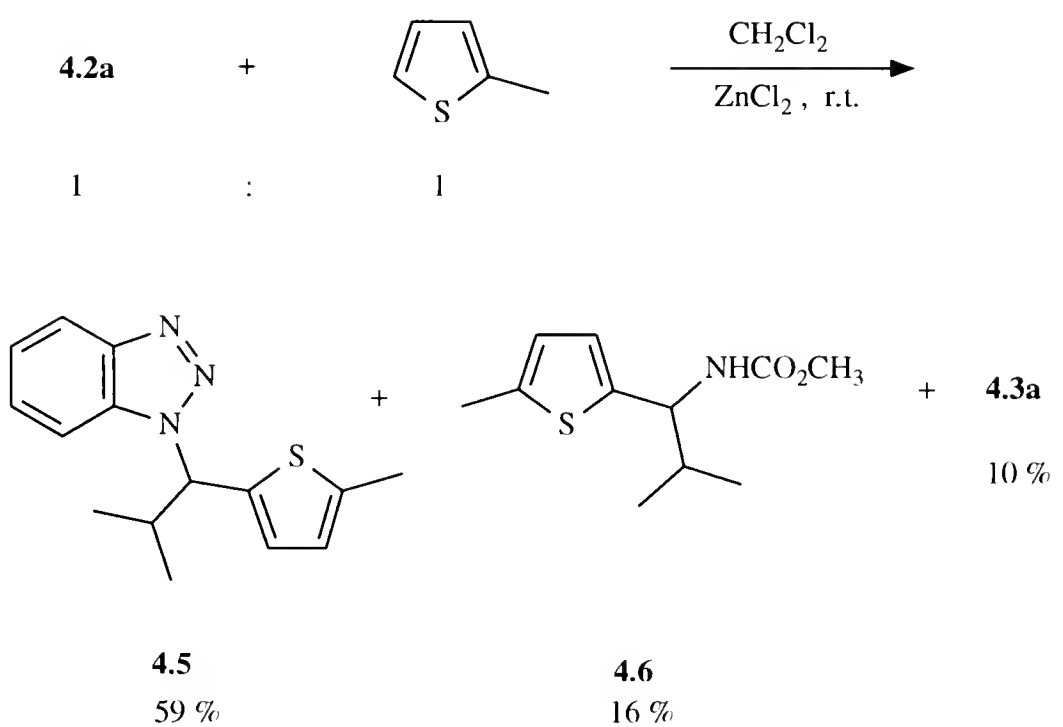
The five symmetrical 1,1-bis(heterocyclyl)methanes (**4.3a-c, 4.4a-b**) were all previously unknown and were characterized by elemental analyses or high resolution mass spectrometry and by ^1H and ^{13}C NMR spectra (Table 4.5 and 4.6).

4.2.3 Preparation of Unsymmetrical Bis-heteroarylalkanes

It is clear that the reactions shown in Scheme 4.2 proceed stepwise. The departure of either benzotriazole or the alkoxyamido group with the assistance of the Lewis acid led to the formation of a carbocation which was stabilized by the remaining carbamate or benzotriazolyl group (*via* the iminium ion). This carbocation then attacks the electron-rich heterocycle ring to give a monosubstituted intermediate. This process is repeated if excess of the heterocycle is present in the solution to produce the symmetrical bis-heteroaromatic methane. Based on this hypothesis, if only one equivalent of a heterocycle was to be added, the monosubstituted intermediate should be formed. If it could be isolated, it should react further with a different heterocyclic molecule, and provide a useful synthetic route to unsymmetrical bis-heteroarylmethanes.

Indeed, when methyl *N*-(α-benzotriazol-1-ylalkyl)carbamate **4.2a** was treated with one equivalent of 2-methylthiophene, a mixture was produced in which a benzotriazole derivative **4.5** predominated, accompanied by methyl *N*-[1-

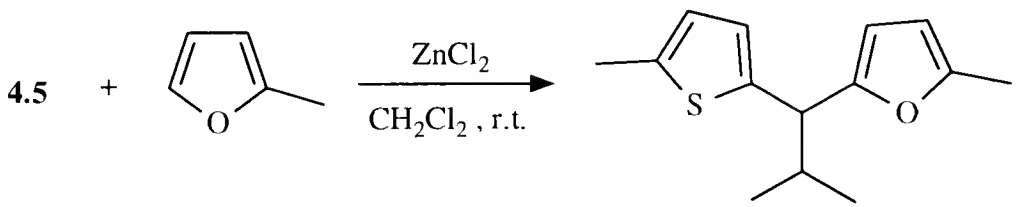
(thiophen-2-yl)-2-methylpropyl]carbamate **4.6**, and the bis(thiophen-2-yl)alkane **4.3a** (Scheme 4.3). 2-Methyl-5-[1-(benzotriazol-1-yl)-2-methylpropyl]thiophene (**4.5**) could be separated either by column chromatography or by recrystallization from $CHCl_3$/hexane. It reacted readily with 2-methylfuran or with 1-methylpyrrole in CH_2Cl_2 in the presence of zinc chloride at room temperature to give the unsymmetrical bis-heteroaryl alkanes **4.7** and **4.8** in 92% and 52% yields (Table 4.7), respectively (Scheme 4.4). In this reaction, the benzotriazole, activated by the



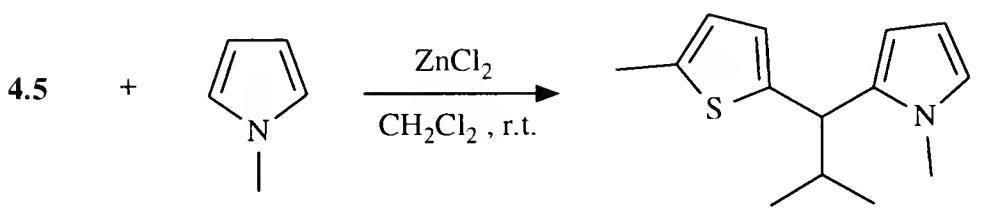
Scheme 4.3

thiophene ring, was readily replaced by a molecule of another heterocycle to afford the desired product. Based on the results illustrated in Scheme 4.2, the

methoxycarbamoyl group is also a suitable leaving group and can also be substituted by a heterocycle, thus the mixture of compounds **4.5** and **4.6** on treatment with 2-methylfuran under the same conditions gave the expected product **4.7** in 95% yield, and with 2-methylpyrrole afforded the compound **4.8** in 65% yield (Scheme 4.5).

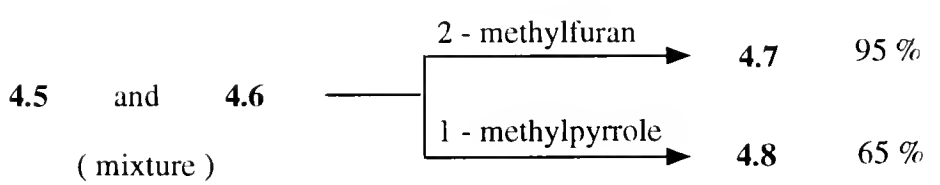


4.7 92 %



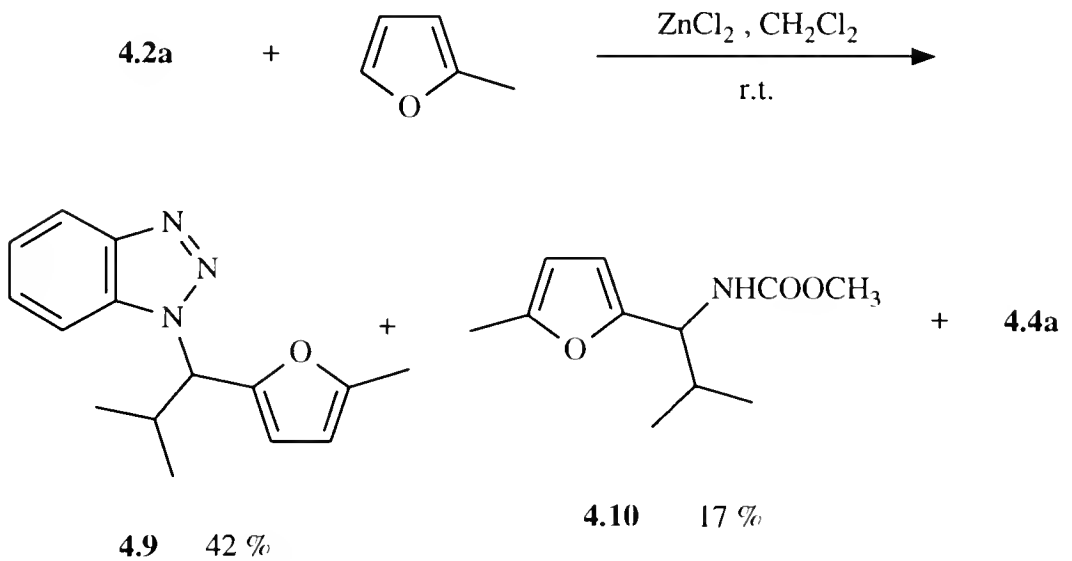
4.8 52 %

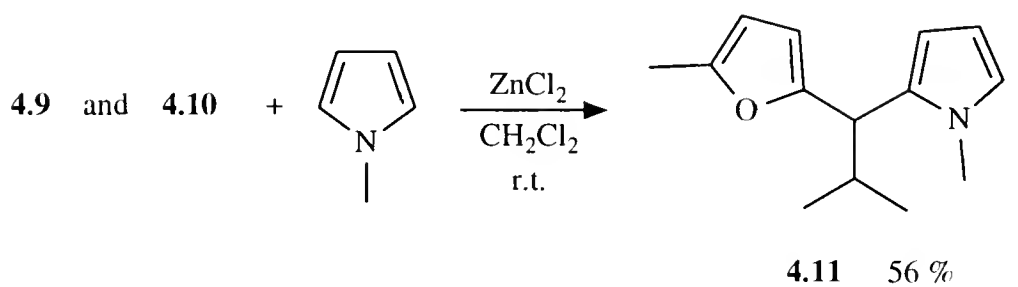
Scheme 4.4



Scheme 4.5

Similarly, when carbamate **4.2a** was treated with one equivalent of 2-methylfuran, a mixture of the benzotriazole derivative **4.9**, methyl *N*-[1-(fur-2-yl)-2-methylpropyl]carbamate **4.10** and the bis-(fur-2-yl)alkane **4.4a** was afforded.

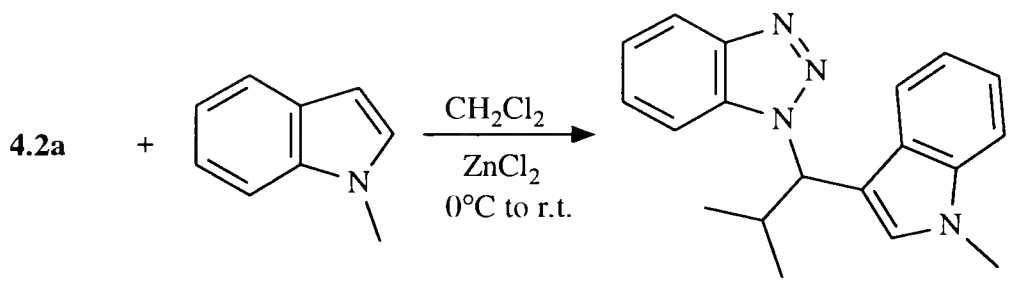




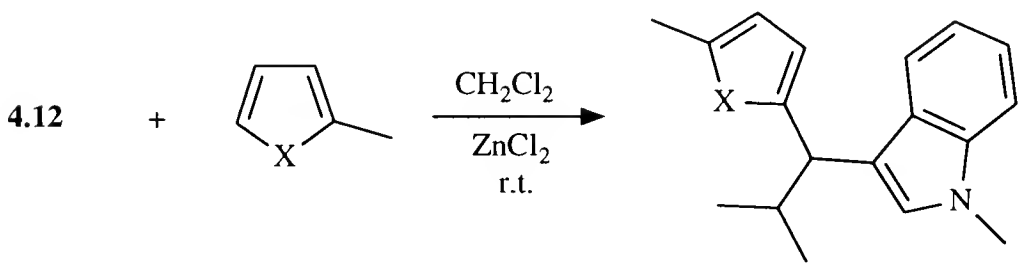
Scheme 4.6

Treatment of the mixture of compounds **4.9** and **4.10** with 1-methylpyrrole in CH_2Cl_2 in the presence of zinc chloride at room temperature gave 1-(1-methylpyrrol-2-yl)-1-(5-methylfur-2-yl)-2-methylpropane **4.11** in 56% yield (Scheme 4.6).

The carbamate **4.2a** reacted with 1-methylindole in a 1:1 ratio in CH_2Cl_2 under the same conditions to give, after recrystallization from $CHCl_3$/hexane, 3-[(α-benzotriazol-1-yl)alkyl]indole **4.12** in 70% yield as the only isolated product. Intermediate **4.12** was then treated further with 2-methylthiophene or with 2-methylfuran at room temperature to afford 3-(α-fur-2-yl)alkyl- (**4.13**) or 3-(α-thiophen-2-yl)alkylindole (**4.14**) respectively in excellent yields (Scheme 4.7).



4.12 70 %

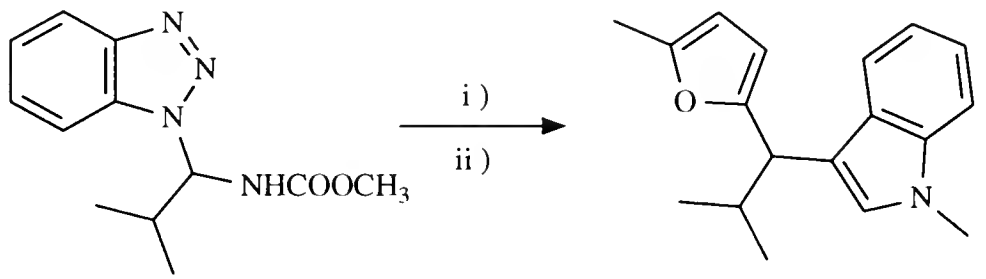


4.13 : X = O 84 %
4.14 : X = S 90 %

Scheme 4.7

In practice, however, it is not necessary to isolate the intermediates and unsymmetrical 1,1-bis-heteroarylalkanes can be prepared from **4.2a** in one-pot procedure. For example, 3-(1-fur-2-yl)alkylindole **4.13** was prepared in 45% yield by

reacting **4.2a** with successive molar equivalents of 1- methylindole and 2-methylfuran as illustrated in Scheme 4.8.



4.2a **4.13**

i) 1-methylindole , $ZnCl_2$, CH_2Cl_2 , r.t.

ii) 2 -methylfuran , $ZnCl_2$, CH_2Cl_2 , r.t.

Scheme 4.8

The proposed structures of the new unsymmetrical bis-heteroaryl alkanes **4.5, 4.7, 4.8, 4.11-4.14** were confirmed by NMR spectroscopy, elemental analyses or high resolution mass spectrometry.

For each of these compounds the α-CH group showed a large coupling (J=8.3-10.4 Hz) to the β-CH in the ^1H spectra. Similarly the α-carbons had a characteristic resonance between δ=43.8-66.1 ppm in the ^{13}C NMR spectra. The features of the NMR spectra of the benzotriazolyl substituted intermediates **4.5** and **4.12** indicated that they were the benzotriazol-1-yl regioisomers. For those products containing either the 2-methylthiophene or 2-methylfuran moieties the two doublets (J = 3.5 Hz) of the two *ortho*-heteroaromatic protons were strong evidence for α-substitution. Likewise the 1H singlet at δ = 6.9ppm in the spectrum of compound

4.13 and **4.14** was indicative of substitution of the 3-position. Detailed assignments of the NMR spectra are listed in Table 4.8, 4.9 and in the experimental section.

We believe that the reaction of α-benzotriazolylalkyl substituted heterocycles with thiophene, furan or indole involved electrophilic attack by the carbocation of type **1.4** which was stabilized by the heteroatom as illustrated in the introduction. Similar to the thioalkylation discussed in Chapter III, Lewis acids assisted the ionization of these benzotriazole derivatives.

The ease with which these carbocations can be formed and their smooth reactions with a variety of heteroaromatics has provided a new and significantly more convenient route to the corresponding bis-heteroarylalkanes. In addition to affording good to excellent yields, this novel methodology also incorporates the advantage of simple removal of the benzotriazole auxiliary from the product mixture by extraction with dilute base.

4.3 Experimental

Melting points were determined with a Kofler hot stage apparatus without correction. ^{1}H and ^{13}C NMR spectra were taken at 300 and 75 MHz, respectively. Tetramethylsilane was used as the internal standard for the ^{1}H NMR spectra, and the central line of $CDCl_3$ ($\delta = 77.0$) or DMSO-d_6 ($\delta = 39.5$) was referenced in ^{13}C NMR spectra.

4.3.1 *N*-(α-Benzotriazolylalkyl)carbamates **4.2a**, **4.2b**, **4.2c** and **4.2d**

They are prepared by the literature procedure (Table 4.1) [90JOC2206].

4.3.2 General Procedure for the Preparation of Symmetrical 1,1-Bis(heteroaryl)-alkanes **4.3a, 4.3b, 4.3c, 4.4a** and **4.4b**

A mixture of *N*-(α-benzotriazolylalkyl)carbamate **4.2** (10 mmol), the heterocycle (22 mmol) and zinc chloride (20 mmol) in dry methylene chloride (50 mmol) was stirred at room temperature overnight and poured into ice-water (50 ml). The water layer was extracted with chloroform (2 x 20 ml). The combined organic layer was washed with NaOH solution (30 ml, 2%) and water (30 ml) and dried over $MgSO_4$ (10 mg). The solvent was evaporated and the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give the pure product (Table 4.4).

4.3.3 2-Methyl-5-[1-(benzotriazol-1-yl)-2-methylpropyl]thiophene (**4.5**)

It was prepared by the procedure described above for symmetrical 1,1-bis(heteroaryl)alkanes from methyl *N*-[1-(benzotriazol-1-yl)-2-methylpropyl]-carbamate (2.5g, 10mmol), 2-methylthiophene (0.98g, 10mmol) and zinc chloride (1.36g, 10mmol). It was purified by recrystallization from $CHCl_3$/hexane (yield 56%). mp. 90-91°C. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.22 (t, J = 8.2 Hz, 1H), 6.85 (d, J = 3.4 Hz, 1H), 6.45 (d, J = 3.4 Hz, 1H), 5.50 (d, J = 10.4 Hz, 1H, CH), 2.96 (m, 1H, CHMe$_2$), 2.28 (s, 3H, CH_3), 1.01 (d, J = 6.6 Hz, 3H, CH_3), 0.72 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR δ 145.8, 140.3, 138.3, 132.4, 126.9, 126.6, 124.4, 123.6, 119.9, 109.7, 66.1 (CH), 33.7, 20.6, 20.5, 19.9. Anal.Calcd for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48. Found: C, 66.47; H, 6.38; N, 15.77. If the crude mixture was separated by column chromatograpy (silica gel, CH_2Cl_2), it gave **4.3a** (10%) and a mixture of **4.5** and **4.6** (59% and 16% respectively based on the ^{1}H NMR).

4.4.4 1-Methyl-3-[1-(Benzotriazol-1-yl)-2-methylpropyl]indole (**4.12**)

1-Methylindole (10 mmol) was added to a mixture of **4.2a** (10 mmol) and $ZnCl_2$ (15 mmole) in dry CH_2Cl_2 (40 ml) at 0°C. The solution was stirred at 0°C for 2h then allowed to warm to room temperature and stirring continued overnight. After work-up as above, the product was purified by column chromatography (silica gel, CH_2Cl_2). (yield 70%). mp.147-148°C, ^1H NMR ($CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38-7.22 (m, 3H), 7.18 (t, J = 6.7 Hz, 1H), 7.08 (t, J = 7.9 Hz, 1H), 5.80 (d, J = 10.2 Hz, 1H, CH), 3.72 (s, 3H, CH_3), 3.23 (m, 1H, CHMe_2), 1.12 (d, J = 6.6 Hz, 3H, CH_3), 0.85 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR δ 145.8, 136.6, 132.8, 127.6, 127.5, 126.9, 123.5, 121.9, 119.8, 119.6, 118.9, 111.9, 109.9, 109.3, 62.9, 32.9, 32.8, 20.9, 20.1. Anal.Calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 75.03; H, 6.67; N, 18.40.

4.4.5 1-(5-Methylfur-2-yl)-1-(5-methylthiophen-2-yl)-2-meth ylpropane (**4.7**); Typical procedure for Unsymmetrical 1,1-Bis(heteroaryl)alkanes **4.7**, **4.8**, **4.11**, **4.13** and **4.14**.

To a solution of either compound **4.5** (2.6g, 10mmol) or a mixture of **4.5** + **4.6** (10mmol) in dry methylene chloride was added 2-methylfuran (0.82g, 10mmol) and zinc chloride (1.4g, 10mmol). The mixture was stirred at room temperature overnight and worked-up as for the symmetrical derivatives. Similarly, **4.8** was prepared from 1-methylpyrrole and either **4.5** or the mixture of **4.5** + **4.6**; compound **4.11** from 2-methylfuran and **4.9** + **4.10**; compound **4.13** from 2-methylfuran and **4.12**; compound **4.14** from 2-methylthiophene and **4.12** (Table 4.7).

4.4.6 One-pot Preparation of 1-(5-Methylfur-2-yl)-1-(1-methylindol-3-yl)-2-methyl-propane (**4.13**)

A mixture of **4.2a** (10 mmol), 1-methylindole (10 mmol) and zinc chloride (10 mmol) in dry methylene chloride was stirred at room temperature overnight. 2-Methylfuran (10 mmol) and zinc chloride (10 mmol) were added and the solution stirred at the same temperature for an additional 10h. The work-up procedure was as described above.

Table 4.1 Preparation of *N*-(1-benzotriazolylalkyl)carbamates

compd	R	R′	mp(°C)	yield(%)	molecular formula	found (required)		
						C	H	N
4.2a	iPr	Me	118-120	84	$C_{12}H_{16}N_4O_2$	58.05 (58.05)	6.53 (6.50)	22.44 (22.57)
4.2b	Ph	Me	123-124	78	$C_{15}H_{14}N_4O_2$	63.87 (63.82)	5.03 (5.00)	19.90 (19.85)
4.2c	H	Me	155-156	74	$C_9H_{10}N_4O_2$	52.38 (52.42)	4.86 (4.89)	27.45 (27.17)
4.2d	Ph	Ph	162-164	69	$C_{20}H_{16}N_4O_2$	69.59 (69.76)	4.73 (4.68)	16.27 (16.27)

Table 4.2 ^{1}H NMR Data of *N*-(1-Benzotriazolylalkyl)carbamates **4.2**

Cpd	Benzotriazole (each H; J, Hz)				NH	OMe	Other Signals
	H4	H5	H6	H7	(1H; J Hz)	(3H,s)	(J Hz)
4.2a	8.10 (d, J=9,0)	7.43 (t, J=7.5)	7.59 (t, J=7.6)	8.08 (d, J=8.4)	8.91 (d, J=8.7)	5.36	6.15(t, J=9.0, 1H), 2.71(m, 1H), 1.18 (d, J=6.6, 3H), 0.57 (d, J=6.6, 3H)
4.2b	8.12 (d, J=8.3)	7.41 (m)[a]	7.56 (t, J=7.9)	7.95 (d, J=8.4)	9.47 (d, J=8.5)	3.64	7.86(d, J=8.6, 1H), 7.41(m, 5H)
4.2c	8.03 (d, J=8.3)	7.39 (t, J=7.6)	7.52 (t, J=6.9)	7.94 (d, J=8.3)	6.55 (s)	3.71	6.06(d, J=6.8, 2H)
4.2d	8.12 (d, J=8.3)	7.44 (m)[a]	7.44 (m)[a]	7.86 (m)[a]	10.0 (d, J=8.5)	-	7.86(m, 2H), 7.44(m, 7H), 7.18(m, 1H), 7.18(m,1H)

[a] Overlapped with Ph-H

Table 4.3 ^{13}C NMR Data of *N*-(1-Benzotriazolylalkyl)carbamates **4.2**

Cpd	Benzotriazole						C=O	other carbons
	C4	C5	C6	C7	C3a	C7a		
4.2a	119.2	127.2	124.0	111.1	145.2	132.0	156.3	71.9(CH), 51.7(OCH_3), 31.4(CH), 19.1(CH_3), 18.2(CH_3)
4.2b	119.2	127.4	124.1	111.1	145.3	131.5	156.1	135.9(Ph), 128.7(Ph), 128.5(Ph), 126.5(Ph), 68.2(CH), 52.1(OCH_3)
4.2c	119.4	127.9	124.4	110.8	146.0	132.4	156.8	53.5(CH_2), 52.8(OCH_3)
4.2d	119.4	127.7	124.3	111.2	145.5	131.7	154.2	150.5(Ph), 135.7(Ph), 129.4(Ph), 129.0(Ph), 128.7(Ph), 126.9(Ph), 125.5(Ph), 121.7(Ph), 68.1(CH)

Table 4.4 Preparation of Symmestry 1,1-Bis(heteroaryl)alkanes **4.3**, **4.4**

Cpd	Heteroaryl	R	mp (°C)	Molecular Formula	HR - MS / Analysis found		HR - MS / Analysis required		Yield (%)
					C	H	C	H	
4.3a	5-methyl-thiophen-2-yl	*i*-Pr	45 - 46	$C_{14}H_{18}S_2$	67.07	7.26	67.15	7.25	90
4.3b	5-methyl-thiophen-2-yl	Ph	oil	$C_{17}H_{16}S_2$	284.0717		284.0694		94
4.3c	5-methyl-thiophen-2-yl	H	oil	$C_{11}H_{12}S_2$	208.0380		208.0380		86
4.4a	5-methyl-fur-2-yl	*i*-Pr	oil	$C_{14}H_{18}O_2$	218.1304		218.1307		88
4.4b	5-methyl-fur-2-yl	Ph	oil	$C_{17}H_{16}O_2$	252.1167		252.1150		90 (65)*

* from phenyl *N*-(1-benzotrazol-1-yl) carbamates **4.2d**

Table 4.5 ^{1}H NMR Data of Symmetrical 1,1-Bis(heteroaryl)alkanes **4.3**, **4.4**

Cpd	heteroaryl	5-methyl (S, 6H)	CH	R
4.3a	6.56(d,J=3.3Hz,2H), 6.50(d,J=3.6Hz,2H)	2.38	3.89(d,J=9.0Hz)	2.17(m,1H,$\underline{CH}Me_2$), 0.94(d,J=6.7Hz,6H)
4.3b	6.56(d,J=3.4Hz,2H), 6.54(d,J=3.3Hz,2H)	2.39	5.66(s)	7.29(d,J=4.2Hz,2H) 7.25(m,3H)
4.3c	6.62(d,J=3.4Hz,2H), 6.54(d,J=3.3Hz,2H)	2.40	4.16(s,2H,CH_2)	-
4.4a	5.96(s,2H), 5.85(s,2H)	2.24	3.68(d,J=8.0Hz)	2.29(m,1H,$\underline{CH}Me_2$), 0.88(d,J=6.8Hz,6H)
4.4b	5.80(s,2H), 5.77(s,2H)	2.02	5.28(s)	7.20-7.08(m,5H,Ph)

Table 4.6 ^{13}C NMR Data of Symmetrical 1,1-Bis(heteroaryl)alkanes **4.3**, **4.4**

Cpd	heteroaryl	5-methyl	CH	R
4.3a	145.5,137.7, 124.2,124.1	15.2	50.5	35.4(CH),21.3(CH_3)
4.3b	145.1,138.9, 125.5,124.4	15.4	47.8	143.6,128.3,128.2,126.8
4.3c	141.1,138.4, 124.7,124.6	15.3	30.5	-
4.4a	153.2,150.2, 106.7,105.8	13.6	46.3	31.2(CH),20.7(CH_3)
4.4b	152.7,151.2, 108.1,105.9	13.7	45.1	139.8,128.3,128.2,126.8

Table 4.7 Preparation of Unsymmestrical 1,1-Bis(Heteroaryl)alkanes **4.7-8**, **4.11**, **4.13-14**

Cpd	Pre-cursor	Yield (%)	Form	Molecular Formula	HR -MS / Analysis found			required		
					C	H	N	C	H	N
4.7	**4.5**	92	oil	$C_{14}H_{18}OS$	234.1071			234.1078		
	4.5 + 4.6	95								
4.8	**4.5**	52	oil	$C_{14}H_{19}NS$	233.1221			233.1238		
	4.5 + 4.6	65								
4.11	**4.9 + 4.10**	56	oil	$C_{14}H_{19}NO$	217.1472			217.1467		
4.13	**4.12**	84	oil	$C_{18}H_{21}NO$	267.1624			267.1623		
	One - Pot	45								
4.14	**4.12**	90	oil	$C_{18}H_{21}NS$	75.95	7.51	4.86	76.28	7.47	4.94

Table 4.8 ^{1}H NMR Data of Unsymmetrical 1,1-Bis(Heteroaryl)alkanes **4.7-8, 4.11, 4.13-14**

Cpd	Het_1	Het_2	CH	iPr
	5-methylthiophen-2-yl	5-methylfur-2-yl		
4.7	6.64(d,J=3.4Hz,1H), 6.53(d,J=3.3Hz,1H), 2.40(s,3H,CH_3)	5.95(d,J=3.1Hz,1H), 5.83(d,J=3.0Hz,1H), 2.24(s,3H,CH_3)	3.75(d, J=8.8Hz)	2.22(m,1H,$CHMe_2$), 0.91(d,J=6.6Hz,3H,CH_3), 0.89(d,J=6.6Hz,3H,CH_3)
	5-methylthiophen-2-yl	1-methylpyrrol-2-yl		
4.8	6.45(d,J=3.3Hz,1H), 6.41(d,J=3.0Hz,1H), 2.32(s,3H,CH_3)	6.40(m,1H), 6.01(d,J=2.1Hz,2H), 3.38(s,3H,NCH_3)	3.60(d, J=9.0Hz)	2.20(m,1H,$CHMe_2$), 0.97(d,J=6.7Hz,3H,CH_3), 0.86(d,J=6.7Hz,3H,CH_3)
	5-methylfur-2-yl	1-methylpyrrol-2-yl		
4.11	5.81(s,2H) , 2.23(s,3H,CH_3)	6.49(t,J=2.3Hz,1H), 6.07(d,J=2.3Hz,2H), 3.48(s,3H,NCH_3)	3.60(d, J=8.5Hz)	2.33(m,1H,$CHMe_2$), 0.94(d,J=6.6Hz,3H,CH_3), 0.89(d,J=6.8Hz,3H,CH_3)
	5-methylfur-2-yl	1-methylindol-3-yl		
4.13	5.95(d,J=2.9Hz,1H), 5.81(d,J=3.0Hz,1H), 2.24(s,3H,CH_3)	7.64(d,J=7.8Hz,1H), 7.24(d,J=7.5Hz,1H), 7.18(d,J=8.0Hz,1H), 7.07(t,J=8.0Hz,1H), 6.96(s,1H,H-2), 3.71(s,3H,NCH_3)	3.90(d, J=8.3Hz)	2.44(m,1H,$CHMe_2$), 0.93(d,J=6.6Hz,3H,CH_3), 0.89(d,J=6.8Hz,3H,CH_3)
	5-methylthiophen-2-yl	1-methylindol-3-yl		
4.14	6.67(d,J=2.9Hz,1H), 6.49(d,J=2.7Hz,1H), 2.37(s,3H,CH_3)	7.62(d,J=7.8Hz,1H), 7.23(d,J=8.0Hz,1H), 7.18(t,J=7.8Hz,1H), 7.07(t,J=8.0Hz,1H), 6.93(s,1H,H-2), 3.69(s,3H,NCH_3)	4.09(d, J=8.5Hz)	2.43(m,1H,$CHMe_2$), 0.98(d,J=6.7Hz,3H,CH_3), 0.95(d,J=6.8Hz,3H,CH_3)

Table 4.9 ^{13}C NMR Data of Unsymmetrical 1,1-Bis(Heteroaryl)alkanes **4.7-8, 4.11, 4.13-4.14**

Cpd	Het_1	Het_2	CH	iPr
	5-methylthiophen-2-yl	5-methylfur-2-yl		
4.7	143.0,137.7,124.5,	154.8,150.4,106.4,	48.3	33.6,
	124.3,15.2(CH_3)	105.8,13.6(CH_3)		21.0,
				20.9
	5-methylthiophen-2-yl	1-methylpyrrol-2-yl		
4.8	145.3,137.9,124.0,	135.2,121.0,106.4,	46.3	33.7,
	123.9,15.3(CH_3)	105.2,22.1(CH_3)		21.2
	5-methylfur-2-yl	1-methylpyrrol-2-yl		
4.11	154.4,150.1,106.5,	132.9,120.9,106.4,	44.2	32.6,
	105.7,13.7(CH_3)	106.3,21.6(CH_3)		21.0
	5-methylfur-2-yl	1-metheylindol-3-yl		
4.13	155.9,149.8,106.0,	136.7,127.7,126.7,121.1,119.5,	43.8	32.7,
	105.6,13.8(CH_3)	118.4,115.2,108.9,21.4(CH_3)		21.3
	5-methylthiophen-2-yl	1-methylindol-3-yl		
4.14	146.9,136.9,124.0,	136.7,127.6,126.2,121.3,119.5,	45.9	34.2,
	123.8,15.4(CH_3)	118.5,117.5,109.0,21.7(CH_3)		21.6

CHAPTER V
INDOLYLALKYLATION. PART I: A VERSATILE SYNTHESIS OF 3-SUBSTITUTED INDOLES

5.1 Introduction

3-Substituted indoles are potential intermediates for many alkaloids and pharmacologically important substances [91JMC140, 89JMC890]. Accordingly, the synthetic elaboration of the indole side chain at the 3-position has been employed as a key step in the synthesis of related alkaloids.

Numerous synthetic approaches to 3-substituted indoles are known, among which, the methods *via* 3-(dimethylaminomethyl)indole [53JA1967, 54CB692] and 3-bromomethylindole [92JHC953] are the most important for introducing and extending functionalized carbon chains at C-3. However, both of these methods are limited to the preparation of compounds in which an unsubstituted methylene group links the indole ring and the nucleophile.

It is well known that deprotonation of the side chains of π-deficient *N*-heteroaromatics (pyridine and quinoline) followed by electrophile quenching is an important synthetic route to side chain functionalization [85HHC1, 84CHC1]. However, methods for metallation of the side chains of π-electron rich heteroaromatics such as indole are much less advanced. Previous work in this laboratory has succeeded in introducing functionality to the 2-alkyl side chain with carbon dioxide [86JA6808], but few other methods are known for the metallation of an alkyl group on C-2 [90JCS(P1)179]. We are aware of only two reports dealing with

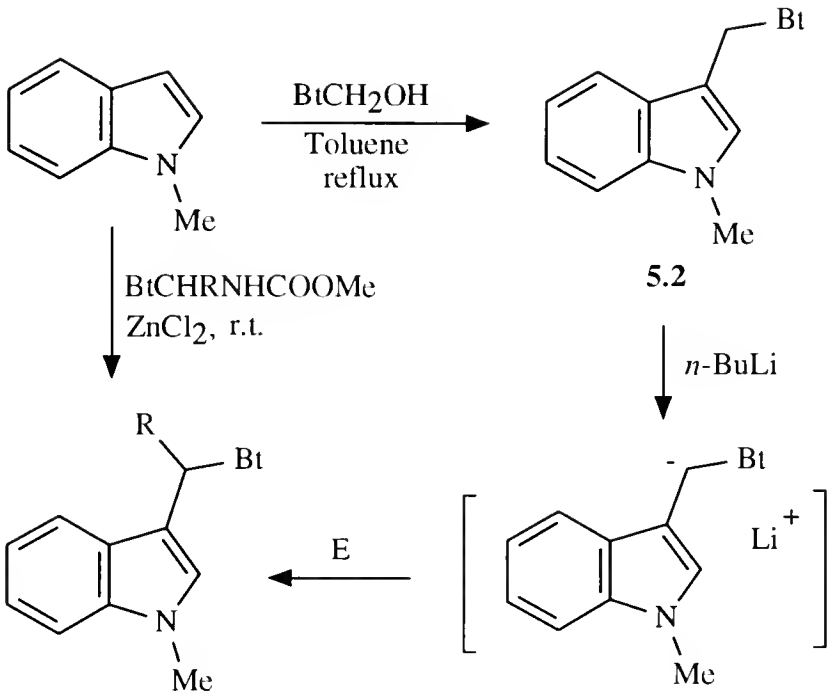
the analogous 3-alkylindole metallation, and both methods are confined to cyano derivatives. Deprotonation of 3-cyanomethylindole by (i) sodium amide in liquid ammonia [62BSF290] and (ii) sodium hydride [74KGS1502] gave a cyano stabilized carbanion which was subsequently quenched by electrophiles.

Work in our laboratory has demonstrated that benzotriazole can sufficiently stabilize an α-carbanion due to its electron-withdrawing ability [91JOC6917]. In Chapter IV, we have described the versatility of benzotriazolylalkyl substituted heterocycles in the synthesis of 1,1-bis-(heteroaryl)alkanes (also see Katritzky *et al* [93JOC4376]). Of these derivatives the utility of 3-(benzotriazolylalkyl)indoles has now been further extended to provide new routes to a wide range of 3-substituted indoles.

5.2 Results and Discussion

Our previous work has shown that 1-methyl-3-(benzotriazol-1-ylalkyl)indole **5.1a** was readily available from the corresponding methyl *N*-(benzotriazol-1-ylalkyl)-carbamate and 1-methylindole (see Chapter IV). Compound **5.1b** was prepared in 58% yield by the same procedure (Scheme 5.1 and Table 5.1). However, this method was limited to the preparation of compounds in which R was an alkyl group.

In order to explore the generality of this methodology, attention was turned to the synthesis of 1-methyl-3-(benzotriazol-1-ylmethyl)indole (**5.2**), which was expected to undergo deprotonation and subsequent reaction with electrophiles to functionalize the side chain at the 3-position. We were unable to access **5.2** by the pathway described above for **5.1a** and **5.1b**, presumably because it is more difficult to form the less stabilized cationic intermediate derived from methyl



5.1	E	R
a	-	*i*-Pr
b	-	Et
c	MeI	Me
d	Me_3SiCl	$SiMe_3$
e	Ph_2CO	$C(Ph)_2OH$
f	PhNCO	C(=O)NHPh

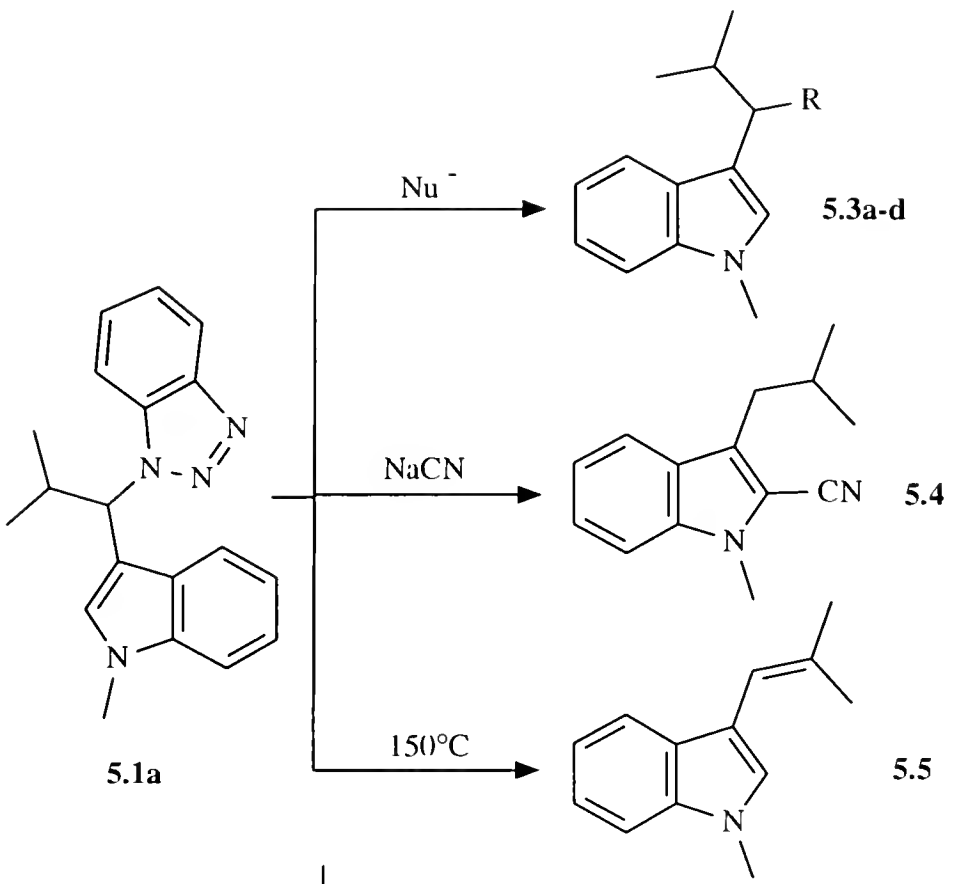
Scheme 5.1

N-(benzotriazol-1-ylmethyl)carbamate [Chapter IV and 93JOC4376]. However, compound **5.2** was prepared by the Mannich type reaction of 1-(hydroxymethyl)-benzotriazole and 1-methylindole in 40% yield. As we expected, deprotonation of **5.2** occurred smoothly with *n*-butyllithium in tetrahydrofuran at -78°C to give the

corresponding anion, which on treatment with methyl iodide and chlorotrimethylsilane gave the corresponding alkylated and silylated products **5.1c** and **5.1d** in yields of 95% and 93%, respectively (Scheme 5.1 and Table 5.1). Using benzophenone and phenyl isocyanate as electrophiles gave, respectively, the corresponding alcohol **5.1e** and amide **5.1f** in excellent yields (Scheme 5.1 and Table 5.1).

1-Methyl-3-(benzotriazol-1-ylalkyl)indoles **5.2** and **5.1b-f** were previously unknown and were characterized by elemental analyses or high resolution mass spectrometry and by ^{1}H and ^{13}C NMR spectroscopy (Tables 5.2, 5.3 and 5.4). The chemical shift of the methine carbon of **5.1d** was upfield of those of the alkylated derivatives **5.1a-c** and **5.1e-f**, due to the shielding effect of silicon. The presence of the chiral center of **5.1e** rendered the two phenyl groups non-equivalent as illustrated by its ^{13}C NMR spectrum, similar to the two methyl groups in **5.1a**.

The benzotriazole moiety in 1-methyl-3-(benzotriazol-1-ylalkyl)indoles **5.1** can be displaced by a variety of nucleophiles. As exemplified by the reactions of **5.1a**, a variety of 3-substituted indoles were prepared (Scheme 5.2 and Table 5.5). Accordingly, treatment of **5.1a** with the sodium salt of thiophenol in refluxing *n*-butanol afforded 1-methyl-3-(1-phenylthio-2-methylpropyl)indole (**5.3a**) in 73% yield, whereas reaction with ethylmagnesium iodide in boiling toluene gave **5.3b** (47%). Compounds **5.3c** (74%) and **5.3d** (53%) were obtained by heating **5.1a** with *N,N*-dimethylaniline or *N*-methylaniline respectively at 150°C. Noteworthy was the fact that, in each case, the substitution occurred exclusively at the *para*-position of the aniline moiety as shown by the AB pattern in the ^{1}H NMR spectra of the products.



5.3	Nu	R
a	NaSPh	SPh
b	EtMgBr	Et
c	$PhNMe_2$	NMe_2
d	PhNHMe	NHMe

Scheme 5.2

This regiospecificity was also observed for 3-(dimethylaminomethyl)indoles [72CHE179].

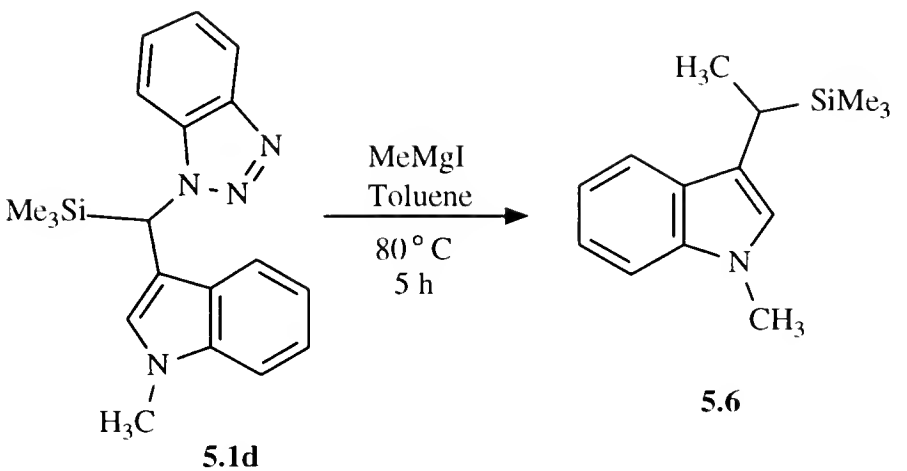
Interestingly, sodium cyanide reacted with **5.1a** to give the indole-2-nitrile **5.4** in 60% yield by an S_N2' cyanide attack, as indicated by the disappearance of the 1H

singlet at *ca* 6.9 ppm for the 2-proton of the indole ring. An analogous result was observed in the displacement of trimethylamine from 3-indolylmethylammonium salt by cyanide ion [72CHE179].

3-Vinylindoles are important intermediates for the synthesis of substituted carbazoles, carbolines and DNA intercalating agents [92JHC953] and are readily available from 3-(benzotriazol-1-ylalkyl)indoles. When compound **5.1a** was heated at 150°C for two days, the product isolated displayed no benzotriazole resonances in the NMR spectra. Furthermore, the presence of a vinylic proton signal illustrated that elimination of benzotriazole had occured to afford the 3-vinylindole **5.5** (50%) (Scheme 5.2 and Table 5.5). Its formation is likely to occur by E1 elimination *via* the carbocation of type **1.4**.

(Trimethylsilylmethyl)arenes have been recognized as versatile intermediates in organic synthesis [82TL5079], but until recently the literature contained no example of the synthesis of (trimethylsilylmethyl)indoles. While Ishibashi *et al* have reported a two-step synthetic sequence using α-chloro-α-silylsulfide, the overall yields are low (highest 34%) [93SC2381]. We now report a readily accessible and high-yielding alternative approach. Heating 1-methyl-3-[(1-trimethylsilyl-1-benzotriazol-1-yl)methyl]indole (**5.1d**) with an excess of methylmagnesium iodide in toluene at 80°C for 5 h gave (1-trimethylsilylalkyl)indole (**5.6**) in excellent yield (Scheme 5.3 and Table 5.5).

It is worthwhile to mention that our attempts to replace the benzotriazolyl group from **5.1e** and **5.1f** were unsuccessful. Upon treatment with thiophenolate **5.1e** reverted back to its starting materials, **5.2** and benzophenone, while the reaction of **5.1e** with active aromatics such as furan in the presence of $ZnCl_2$ in CH_2Cl_2 resulted in a complicated mixture, probably due to the existence of the labile hydroxy group.



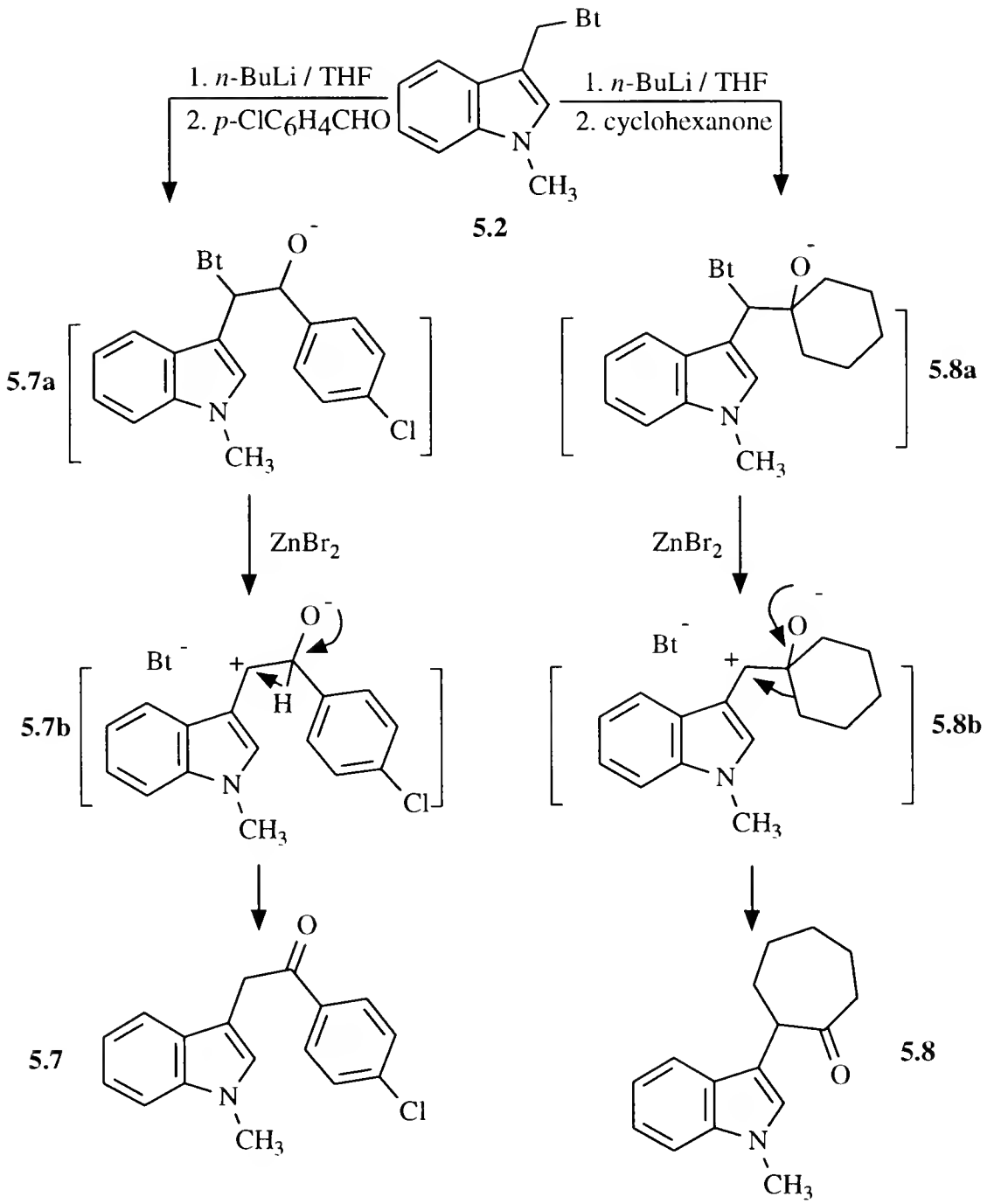
5.1d **5.6**

Scheme 5.3

On the other hand, treatment of **5.1f** either with thiophenolate in refluxing ethanol or with 2-methylfuran under Lewis acid conditions always led to the total recovery of the starting materials. This result indicated that compound **5.1f** is not reactive towards nucleophilic substitution due to the existence of the electron-withdrawing group, the amide group, which is in agreement with the carbocation mechanism discussed above.

Results shown in Chapter III and IV have demonstrated that $ZnBr_2$ can enhance the leaving ability of benzotriazolyl group. Following a similar protocol, interestingly, α-indol-3-yl ketones, **5.7** and **5.8**, were readily prepared in good yields in one-pot by the subsequent addition of $ZnBr_2$ to the reaction mixture of lithiated 1-methyl-3-(benzotriazol-1-ylmethyl)indole **5.2** with *p*-chlorobenzaldehyde or cyclohexanone (Scheme 5.4, Table 5.5).

These results might be explained in terms of the formation of the carbocations **5.7b** and **5.8b** with the assistance of $ZnBr_2$, and their subsequent rearrangements. In the case of *p*-chlorobenzaldehyde, hydride shift gave ketone **5.7**, while in the case of cyclohexanone, compound **5.8** was afforded *via* the ring expansion.


Bt
1. n-BuLi / THF
2. p-ClC6H4CHO
1. n-BuLi / THF
2. cyclohexanone
N
CH3
5.2
5.7a
5.8a
ZnBr2
ZnBr2
5.7b
5.8b
5.7
5.8
Cl
O
H

Scheme 5.4

The structures of indole derivatives **5.3a-d**, **5.4**, **5.5**, **5.6**, **5.7** and **5.8** were confirmed by the ^{1}H and ^{13}C NMR data and by CHN microanalyses or high resolution mass spectrometry. For **5.3a-d**, the chiral center induced magnetic non-equivalence of the two methyl groups in the adjacent *iso*-propyl group, as indicated by their ^{1}H NMR and / or ^{13}C NMR spectra. Detailed assignments of the NMR data are given in Tables 5.6 and 5.7.

5.3 Experimental

Melting points were determined with a Kofler hot stage apparatus without correction. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Tetramethylsilane was used as the internal standard for the ^{1}H NMR spectra, and the central line of $CDCl_3$ (δ = 77.0) or DMSO-d_6 (δ = 39.5) was referenced in the ^{13}C NMR spectra.

5.3.1 1-Methyl-3-(benzotriazol-1-ylalkyl)indoles **5.1a** and **5.1b**

They were prepared by the literature procedure [Chapter IV and 93JOC4376].

5.3.2 General Procedure for the Preparation of 1-Methyl-3-(benzotriazol-1-ylalkyl)-indoles **5.1c-f**

To a solution of **5.2** (1.2 g, 4.6 mmol) in THF (50 ml) was added *n*-butyllithium (2.5 M in hexanes; 2.0 ml, 5.0 mmol) at - 78°C. The solution was stirred at - 78°C for 1 h, and a solution of the corresponding electrophile (5.0 mmol) in THF (8 ml) was added. The reaction mixture was stirred at - 78°C for 2 h, poured into saturated aqueous NH_4Cl (40 ml), and the aqueous layer extracted with Et_2O (3 ×

30 ml). The organic layer was then washed with H_2O and dried ($MgSO_4$). The solvent was removed to afford the crude product, which was purified by column chromatography (silica gel, CH_2Cl_2) to give pure product.

5.3.3 1-Methyl-3-(benzotriazol-1-ylmethyl)indole **5.2**

A mixture of 1-methylindole (3.93 g, 30 mmol) and 1-(hydroxymethyl)-benzotriazole (6.7 g, 45 mmol) in toluene (150 ml) was refluxed for 40 h. After the solvent was evaporated, the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give the pure product (40%), mp 153-154°C.

5.3.4 1-Methyl-3-(1-phenylthio-2-methylpropyl)indole **5.3a**

To a solution of thiophenol (0.55 g, 5 mmol) and sodium metal (0.12 g, 5 mmol) in *n*-butanol (50 ml) **5.1a** (0.91 g, 3 mmol) was added and the mixture refluxed for 50 h. *n*-Butanol was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (30 ml), washed with water (2 × 10 ml) and dried ($MgSO_4$). The solvent was then evaporated and the residue purified by column chromatography (silica gel, CH_2Cl_2 : hexanes = 1 : 1) to give the pure product (73%).

5.3.5 1-Methyl-3-(1-ethyl-2-methylpropyl)indole **5.3b**

To a solution of **5.1a** (0.91 g, 3 mmol) in toluene (50 ml) was added a solution of ethylmagnesium iodide (10 mmol) in Et_2O (10 ml). The mixture was refluxed for 1.5 h, poured into saturated aqueous NH_4Cl (40 ml), and the aqueous layer extracted

with Et_2O (3 × 30 ml). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (silica gel, hexanes) to give a colorless oil (47%).

5.3.6 1-Methyl-3-[1-(4-*N,N*-dimethylamino)phenyl-2-methyl]propylindole **5.3c**

To a small vial **5.1a** (0.4 g, 1.3 mmol) and *N,N*-dimethylaniline (0.24 g, 2 mmol) were added. The mixture was heated in an oil bath at 150°C for 2 days and then separated by column chromatography (silica gel, hexanes : ethyl acetate = 1 : 1) to give the pure product (74%).

5.3.7 1-Methyl-3-[1-(4-*N*-methylamino)phenyl-2-methyl]propylindole **5.3d**

To a small vial **5.1a** (0.25 g, 0.8 mmol) and *N*-methylaniline (0.13 g, 1.2 mmol) were added. The mixture was heated in an oil bath at 150°C for 2 days and then separated by column chromatography (silica gel, hexanes : ethyl acetate = 3 : 1) to give the pure product (53%).

5.3.8 1-Methyl-2-cyano-3-(2-methylpropyl)indole **5.4**

To a solution of **5.1a** (0.6 g, 2 mmol) in DMF (40 ml) was added sodium cyanide (0.2 g, 4 mmol). The mixture was stirred at 130°C for 50 h. Ethyl acetate (60 ml) was added and the mixture washed with water (4 × 40 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column

chromatography (silica gel, CH_2Cl_2 : hexanes = 1 :1) to yield the pure product (60%) as a colorless oil.

5.3.9 1-Methyl-3-(2-methylpropen-1-yl)indole **5.5**

A solution of **5.1a** (0.91 g, 3 mmol) in DMF (20 ml) was heated at 150°C for 2 days. Ethyl acetate (30 ml) was added and the mixture washed with water (3 × 30 ml). The organic layer was dried ($MgSO_4$) and the solvent removed. The residue was separated by column chromatography (silica gel, CH_2Cl_2 : hexanes = 1 : 1) to afford the pure product (50%) as a colorless oil.

5.3.10 1-Methyl-3-(1-trimethylsilylethyl)indole **5.6**

To a solution of **5.1d** (1.0 g, 3 mmol) in toluene (50 ml) was added a solution of methylmagnesium iodide (8 mmol) in Et_2O (10 ml). The mixture was heated at 80°C for 5 hours. The reaction mixture was then poured into saturated aqueous NH_4Cl (40 ml), and the aqueous layer extracted with Et_2O (3 x 30 ml). The organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography (silica gel, hexanes) to give a white solid (90%).

5.3.11 [1-Methyl-3-(4-chlorobenzoyl)methyl]indole **5.7** and [1-methyl-3-(2-oxocarbo-heptyl)]indole **5.8**; General procedure

To the solution of **5.2** (1g, 3.82 mmol) in THF (40 ml) was added *n*-butyllithium (2M in cyclohexane; 2.1 ml, 4.2 mmol) at -78°C under argon. The solution was stirred at -78°C for 1 h, and a solution of aldehyde or ketone (4.2 mmol)

in THF (10 ml) was added. The reaction mixture was stirred at this temperature for further 2 h and a solution of $ZnBr_2$ (0.95g, 4.2 mmol) in THF (10 ml) was added. The mixture was allowed to warm to r.t. overnight and then refluxed for 6 h. After aqueous work-up, the crude product was purified by column (silica gel, hexanes : ethyl acetate = 2 : 1) to yield the pure product.

Table 5.1 Preparation of Adducts **5.1a-f** and **5.2**

Compd	Yield (%)	Method	mp (°C)
5.1a [d]	70	*b*	147-148
5.1b	58	*b*	131-132
5.1c	95	*c*	oil
5.1d	93	*c*	176-177
5.1e	91	*c*	214-215
5.1f	90	*c*	233-234
5.2	40	*a*	153-154

[a] Condensation of 3-methylindole with $BtCH_2OH$.

[b] Condensation of 3-methylindole with *N*-(benzotriazol-1-yl)-carbamates.

[c] Lithiation / elctrophile-quenching of **5.2**

[d] Previously obtained and characterized (Chapter IV)

Table 5.2 Microanalyses / HRMS Data of Adducts **5.1a-f** and **5.2**

Compd	Molecular Fomula	Analysis / HRMS					
		C	H	N	C	H	N
		required			found		
5.1a	$C_{19}H_{20}N_4$	[Chapter IV]					
5.1b	$C_{18}H_{18}N_4$	74.46	6.25	19.30	74.66	6.34	19.34
5.1c	$C_{17}H_{16}N_4$	276.1375			276.1365		
5.1d	$C_{19}H_{22}N_4Si$	68.22	6.63	16.75	68.02	6.74	16.50
5.1e	$C_{29}H_{24}N_4O$	78.36	5.44	12.60	78.30	5.47	12.67
5.1f	$C_{23}H_{19}N_5$	72.42	5.02	18.36	72.13	5.03	18.33
5.2	$C_{16}H_{14}N_4$	73.26	5.38	21.36	73.18	5.37	21.44

Table 5.3. ^{1}H NMR Data of 1-Methyl-3-(benzotriazol-1-ylalkyl)indoles **5.1b-f, 5.2**

Cpd	NCH_3 (s, 3H)	Bt - CH_2 or BtCH	Other Signals
5.1b	3.71	6.19(dd, 1H, J_1=9.3, J_2=6.1)	8.00(d, 1H, J=7.4), 7.45-7.41(m, 2H), 7.30-7.13(m, 5H), 6.98 (t, 1H, J=7.9), 2.72-2.58(m, 2H), 0.94(t, 3H, J=7.3)
5.1c	3.63	6.39(q, 1H, J=7.1)	7.95-7.88(m, 1H), 7.25-7.05(m, 7H), 6.88(t, 1H, J=6.9), 2.06 (d, 3H, J=7.1)
5.1d	3.18	5.06(s, 1H)	7.53(dd, 1H, J_1=6.6, J_2=2.7), 7.05(d, 1H, J=7.9), 6.89-6.83 (m, 1H), 6.79-6.73(m, 4H), 6.63(t, 1H, J=8.1), 6.42(s, 1H), -0.20 (s, 9H)
5.1e	3.62	6.59(s, 1H)	8.23(d, 1H, J=8.3), 7.78(m, 4H), 7.61(m, 2H), 7.43(m, 3H), 7.21 (m, 4H), 7.04(m, 5H), 3.37(s, 1H)
5.1f	3.84	7.64(s, 1H)	10.75(s, 1H), 7.94(dd, 1H, J_1=6.95, J_2=1.7), 7.67(m, 2H), 7.57 (dd, 1H, J_1=8.3, J_2=2.6), 7.30(m, 5H), 7.15(t, 1H, J=7.2), 7.08 (t, 1H, J=7.2), 6.98(t, 1H, J=7.2)
5.2	3.68	5.96(s, 2H)	8.00(d, 1H, J=8.0), 7.62(d, 1H, J=7.9), 7.44(d, 1H, J=8.0), 7.34 -7.19(m, 4H), 7.10-7.07(m, 2H)

Table 5.4 ^{13}C NMR Data of 1-Methyl-3-(benzotriazol-1-ylalkyl)indoles **5.1b-f, 5.2**

Cpd	benzotriazole			indole				$BtCH_2$ or BtCH	NCH_3	Other Signals
	C4	C5	C6	C2	C3	C4	C5			
	C7	C3a	C7a	C6	C7	C3a	C7a			
5.1b	119.5	126.6	123.5	126.8	112.6	119.8	122.0	58.7	32.8	27.2, 11.3
	110.2	146.3	132.3	118.8	109.3	126.8	136.9			
5.1c	119.7	126.6	123.5	122.1	113.5	118.8	119.6	56.7	32.8	20.2
	110.4	146.4	131.9	118.8	109.4	126.1	137.1			
5.1d	119.5	126.7	123.5	126.5	111.5	119.2	121.7	47.7	32.7	-1.83
	110.3	145.9	133.5	118.7	109.3	126.7	136.5			
5.1e	119.1	127.9	125.5	123.5	112.9	118.3	121.2	62.2	32.5	145.3, 144.7,
	109.7	145.7	131.2	118.6	108.1	127.3	135.4			133.1, 127.5,
										126.6, 126.5,
										126.5, 126.1,
										81.6
5.1f	118.8	126.6	123.3	123.7	112.3	119.4	121.9	59.9	32.6	165.5, 138.2,
	109.8	145.7	132.6	118.0	106.1	126.4	136.6			129.5, 128.5,
										119.5
5.2	119.6	126.8	123.5	126.6	109.4	119.7	122.1	44.0	32.6	
	109.8	146.1	132.5	118.7	108.0	128.1	136.9			

Table 5.5 Preparation of 3-Substituted Indoles **5.3a-d**, **5.4-8**

Cpd	Yield (%)	mp (°C)	Molecular Formula	HR-MS / Analysis found C	found H	found N	required C	required H	required N
5.3a	73	oil	$C_{19}H_{21}NS$	77.26	7.22	4.93	77.24	7.16	4.74
5.3b	47	oil	$C_{15}H_{21}N$	215.1652			215.1674		
5.3c	74	97-98	$C_{21}H_{27}N_2$	307.2131			307.2174		
5.3d	53	112-113	$C_{20}H_{24}N_2$	293.2022			293.2018		
5.4	60	oil	$C_{14}H_{16}N_2$	212.1316			212.1313		
5.5	50	oil	$C_{13}H_{15}N$	185.1167			185.1204		
5.6	90	55-56	$C_{14}H_{21}NSi$	231.1457			231.1443		
5.7	70	114-115	$C_{17}H_{14}NOCl$	71.63	4.91	4.79	71.96	4.97	4.94
5.8	76	oil	$C_{16}H_{19}NO$	79.27	8.03	5.92	79.63	7.94	5.80

Table 5.6. ^{1}H NMR Data of 3-Substituted Indoles **5.3a-d**, **5.4-5.8**

Cpd	NCH_3 (s, 3H)	$InCH_2$ or InCH	Other Signals
5.3a	3.63	4.45(d, 1H, J=5.9)	7.69(d, 1H, J=7.8), 7.27-7.22(m, 4H), 7.20-7.05(m, 4H), 6.93(s, 1H), 2.35-2.33(m, 1H), 1.05(d, 6H, J=6.6)
5.3b	3.68	2.53-2.45 (m, 1H)	7.52(d, 1H, J=7.9), 7.19-6.95(m, 3H), 6.65(s, 1H), 1.94-1.87(m, 1H), 1.72-1.58(m, 2H), 0.85(t, 3H, J=6.1), 0.75(d, 3H, J=7.0), 0.70(d, 3H, J=7.0)
5.3c	3.60	3.71(d, 1H, J=9.5)	7.57(d, 1H, J=8.8), 7.20-7.12(m, 4H), 7.02(t, 1H, J=7.6), 6.87(s, 1H), 6.62(d, 2H, J=7.3), 2.81(s, 6H), 2.45-2.42(m, 1H), 0.99(d, 3H, J=6.6), 0.89(d, 3H, J=6.5)
5.3d	3.54	3.61(d, 1H, J=9.5)	7.47(d, 1H, J=8.8), 7.11-7.00(m, 4H), 6.90(t, 1H, J=7.6), 6.79(s, 1H), 6.37(d, 2H, J=8.5), 3.21(br.s, 1H), 2.60(s, 3H), 2.34-2.29(m, 1H), 0.90 (d, 3H, J=6.6), 0.78(d, 3H, J=6.6)
5.4	3.82	2.77(d, 2H, J=7.3	7.62(d, 1H, J=7.3), 7.39(t, 1H, J=7.3), 7.30(d, 1H, J=7.3), 7.18(t, 1H, J=7.3), 2.09-2.04(m, 1H), 0.96(d, 6H, J=6.7)
5.5	3.72	6.40(s, 1H)	7.63(d, 1H, J=7.0), 7.24-7.10(m, 3H), 6.98(s, 1H), 1.96(s, 3H), 1.91 (s, 3H)
5.6	3.73	2.44(q, 1H, J=7.7)	7.55(d, 1H, J=7.9), 7.27(d, 1H, J=7.9), 7.22(t, 1H, J=7.9), 7.08(t, 1H, J=7.9), 6.71(s, 1H), 1.41(d, 3H, J=7.7), 0.00(s, 9H)
5.7	3.68	4.32(s, 2H)	7.95(d, 2H, J=6.8), 7.57(d, 1H, J=7.9), 7.36(d, 2H, J=6.8), 7.23(m, 2H), 7.13(t, 1H, J=7.9), 6.93(s, 1H)
5.8	3.73	4.04(dd, 1H, J=11.3 and 4.7)	7.67(d, 1H, J=9.9), 7.28-7.19(m, 2H), 7.11(t, 1H, J=8.0), 7.00(s, 1H), 2.79-2.70(m, 1H), 2.45-2.24(m, 2H), 2.04-1.92(m, 4H), 1.50-1.43 (m, 3H)

Table 5.7. ^{13}C NMR Data of 3-Substituted Indoles **5.3a-d, 5.4-8**

Cpd	Indole				NCH_3	$InCH_2$ or InCH	Other Signals
	C2	C3	C4	C5			
	C6	C7	C3a	C7a			
5.3a	125.9	114.2	118.8	121.4	33.3	52.5	130.6, 128.9, 128.5, 128.0, 32.6,
	119.6	109.2	127.2	137.0			20.8, 20.1
5.3b	126.2	117.2	118.1	121.0	32.5	45.3	25.4, 22.7, 21.0, 20.4, 12.8
	119.7	108.9	128.6	137.0			
5.3c	125.5	118.9	118.3	121.1	32.9	49.9	148.7, 133.5, 128.7, 112.6, 40.7,
	119.6	108.8	128.0	136.8			32.4, 22.2, 21.7
5.3d	125.5	119.0	118.3	121.1	32.9	50.0	147.1, 134.0, 128.9, 112.2, 32.5,
	119.6	108.8	128.0	136.7			30.8, 22.2, 21.6
5.4	126.0	113.7	109.8	125.7	34.1	31.3	120.3, 29.7, 22.4
	120.7	109.7	127.4	137.9			
5.5	126.5	113.1	118.9	121.7	32.7	132.1	115.6, 26.8, 20.3
	119.1	108.9	127.9	136.3			
5.6	124.3	119.2	119.6	121.1	32.6	18.7	15.9, -2.9,
	117.9	108.8	127.9	136.6			
5.7	127.6	109.3	118.7	121.8	32.6	35.5	196.5, 136.9, 134.9, 130.0, 128.8
	119.2	106.9	127.7	139.3			
5.8	126.2	113.3	119.0	121.7	32.6	50.4	213.1, 41.2, 31.3, 30.0, 28.1, 25.6
	119.5	109.1	127.1	136.9			

CHAPTER VI

INDOLYLALKYLATION. PART II: A GENERAL AND FACILE SYNTHESIS OF HETEROCYCLO[B]-FUSED CARBAZOLES

6.1 Introduction

Heterocyclo[b]-fused carbazole systems are of great importance as they are present in many natural products [88MI3, 85MI1]. Moreover, many heterocycle-fused carbazoles, such as pyridocarbazoles and indolocarbazoles have proven to possess very interesting biological activities [88MI3, 86MI1673, 85MI1].

Although several synthetic routes to indolo[b]carbazoles are reported [92JHC1237, 89AP451, 70T3353, 63JCS3097, 61JOC1509], they usually used either some inconvenient reagents or tedious procedures. Furthermore, they are only confined to indolocarbazole systems. There are no general methods available in the literature for the synthesis of heterocyclo[b]-fused carbazoles. In fact, thieno[b]-carbazole and furo[b]carbazole systems remain unknown previously. Their supposed inaccessibility is a possible explanation.

Herein we delineate a general and facile approach for the construction of heterocyclo[b]-fused carbazoles: indolo[b]carbazole, thieno[b]carbazole, and furo[b]-carbazole ring systems using readily available 1-methyl-3-[(benzotriazol-1-yl)-methyl]indole (**5.2**) as the precursor. Work in Chapter IV has demonstrated the versatility of benzotriazolylalkyl substituted heterocycles in the synthesis of 1,1-bis-(heteroaryl)alkanes [93JOC4376]. Of these derivatives the utility of 1-methyl-3-

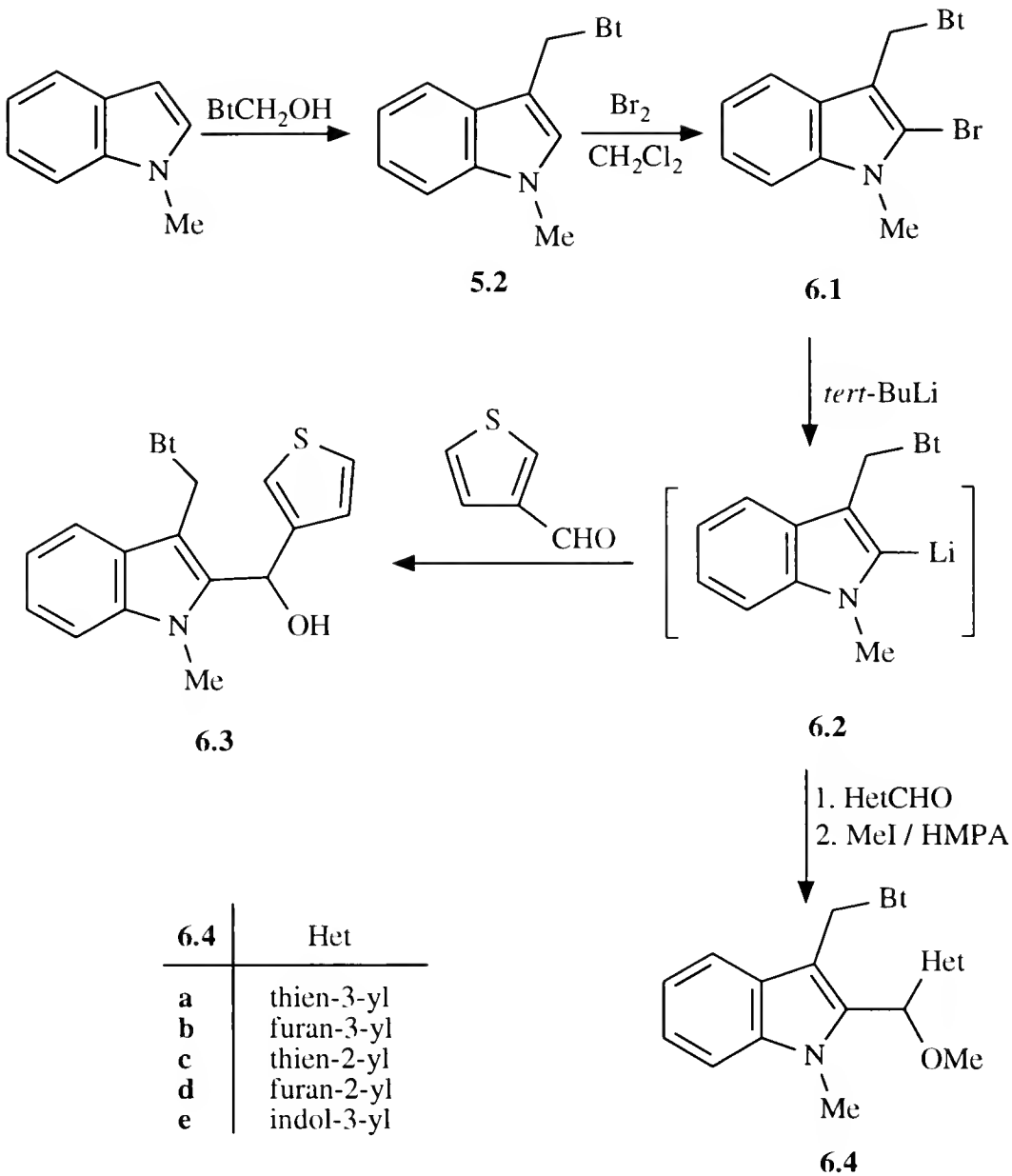
[(benzotriazol-1-yl)methyl]indole (**5.2**) has been especially extended to the synthesis of a wide range of 3-substituted indoles as described in Chapter V. Compound **5.2** has now been further developed to provide an efficient route to various heterocyclo[b]-fused carbazoles.

6.2 Results and Discussion

The requisite 1-methyl-3-[(benzotriazol-1-yl)methyl]indole (**5.2**) was prepared in 40% yield from 1-methyl indole as described in Chapter V.

One of the key steps to heterocyclo[b]-fused carbazoles **6.7** is the generation of the 2-lithio derivative **6.2** as shown in Scheme 6.1. Although the 2-lithiation directly from indoles has been well documented [53JA375, 73JOC3324, 89H745], the lithiation of 1-methyl-3-[(benzotriazol-1-yl)methyl]indole (**5.2**) always occurs regiospecifically at the side chain due to the electron withdrawing nature of the benzotriazolyl group as demonstrated by our previous observations (see Chapter V).

Thus, 2-bromoindole **6.1** was chosen as our target molecule for the regiospecific generation of 2-lithioindole **6.2** since halogen-metal exchange methodology has been efficiently used for the formation of reactive carbanions [92H2095, 83JOC2690]. Regioselective bromination of **5.2** was readily accomplished using bromine as the reagent in CH_2Cl_2. Accordingly, 2-bromoindole **6.1** was obtained in 81% yield. That this bromination is regioselective in the desired sense was indicated by the disappearance of the 1H singlet (2-proton of indole) at *ca* 7.0 ppm in the ^1H NMR spectrum of **6.1**.



6.4	Het
a	thien-3-yl
b	furan-3-yl
c	thien-2-yl
d	furan-2-yl
e	indol-3-yl

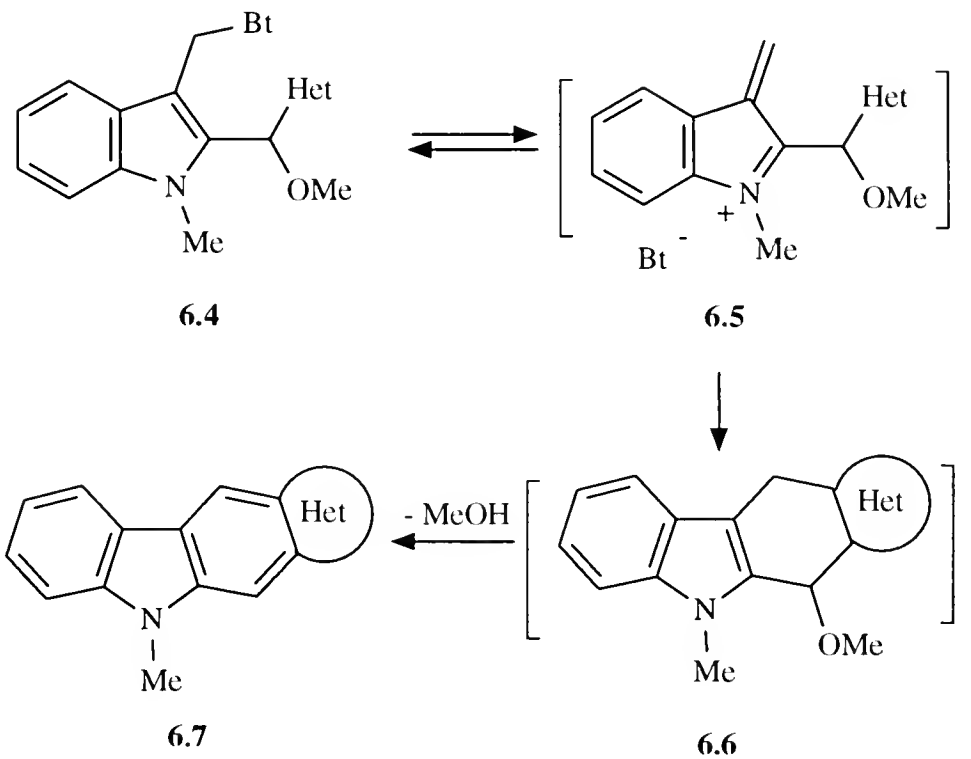
Scheme 6.1

In accord with expectations, the lithiation of **6.1** occurred exclusively at 2-position to form 1-methyl-2-lithio-3-[(benzotriazol-1-yl)methyl]indole (**6.2**),

without any detectable side chain lithiation. Thus, treating **6.1** with 1.2 equiv of *tert*-butyllithium (-78°C, THF) resulted in the immediate formation of a deep brown color due to the anion **6.2**. After 5 min this solution was treated with thiophene-3-carboxaldehyde, furan-3-carboxaldehyde, thiophene-2-carboxaldehyde, furan-2-carboxaldehyde and indole-3-carboxaldehyde respectively, followed by the protection of the oxygen anion formed with methyl iodide and HMPA to give the intermediate products **6.4a-e** in excellent yields (Table 6.1). The structures of **6.4a-e** are confirmed by elemental analyses and NMR spectra data. In these compounds, the chiral center induces magnetic non-equivalence of the two protons of the methylene group adjacent to the benzotriazole and indole rings, as indicated by the two doublets at *ca* 6.0 ppm in their ^{1}H NMR spectra. Detailed assignments of the NMR data are given in experimental section.

As discussed in previous chapters, various types of benzotriazole derivatives reversibly ionize to yield the benzotriazolyl anion and the corresponding carbocations and the ionization can be efficiently facilitated by Lewis acids. Due to such ionization, the benzotriazole auxiliary group can be displaced by different nucleophiles. By analogy with other benzotriazole derivatives, compounds **6.4** presumably exist in equilibrium with ion pairs **6.5** under certain reaction conditions (Scheme 6.2), which should react intramolecularly to furnish the cyclized products. Accordingly, we first employed Lewis acid conditions to effect the cyclization. Unfortunately, compounds **6.4** were very unstable in the presence of Lewis acid such as zinc bromide even at low temperature (-10°C) and immediately led to oligomers. This result however is not very surprising as the existence of the Lewis acid greatly enhances the leaving ability of the methoxy group and the cations formed due to its departure react intermolecularly to lead to polymerized products.

After the unsuccessful attempts to cyclize under Lewis acid conditions, we examined high temperature methodology as a means with which to effect the desired ionization and ring closure and we found that it was very successful. Thus, refluxing



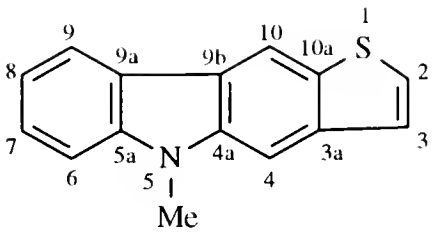
Scheme 6.2

the solution of compounds **6.4a-d** respectively in 1,2,4-trichlorobenzene (*ca* 216°C) for 2 days furnished the corresponding expected products 5-methylthieno[3,2-b]-carbazole (**6.7a**), 5-methylfuro[3,2-b]carbazole (**6.7b**), 5-methylthieno[2,3-b]-carbazole (**6.7c**) and 5-methylfuro[2,3-b]carbazole (**6.7d**) in good yields (Table 6.2). Compound **6.4e** is less stable and more reactive than **6.4a-d** and its cyclization was accomplished by refluxing in 1,2-dichlorobenzene (*ca* 180°C) to give 5,11-dimethylindolo[3,2]carbazole (**6.7e**) in 32% yield. These transformations are

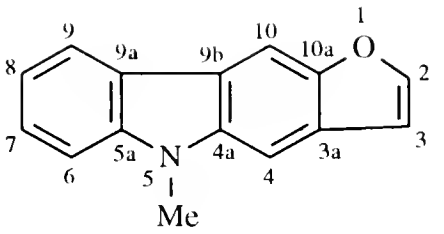
envisioned to proceed *via* intramolecular cyclization to form intermediates **6.6**, which undergo aromatization *in situ* by losing a molecule of methanol to afford the desired products **6.7**. Fused carbazoles **6.7a-d** are new and thieno[3,2-b]carbazole, thieno-[2,3-b]carbazole, furo[3,2-b]carbazole and furo[2,3-b]carbazole are previously unknown tetracyclic condensed systems. Their structures (see Scheme 6.3) are fully supported by elemental analyses and NMR spectra data (see experimental section). The two 1H singlets (4,10-protons) in the region of 7.4-8.5 ppm in the ^{1}H NMR spectra are characteristics of the fused carbazole ring systems **6.7a-d**. 5,11-Dimethylindolo[3,2-b]carbazole (**6.7e**) is known previously [76LA1090] and its structure is also confirmed by CHN analysis and NMR spectra data (see experimental section). A 2H singlet at 7.93 ppm (6,12-protons) in the ^{1}H NMR spectrum is indicative of the symmetrical structure of the indolo[3,2-b]carbazole **6.7e**.

It is worthwhile to mention that our attempted cyclization from compound **6.3**, which was prepared in 91% yield in the similar way as **6.4** without subsequent protection of the oxygen anion as shown in Scheme 6.1, was unsuccessful and no pure compound **6.7a** was isolated although trace of the product was detected by ^{1}H NMR spectroscopy. The existence of the labile hydroxy group might be responsible for the complexities.

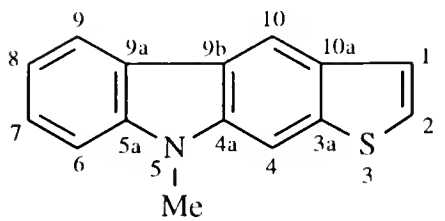
In conclusion, a general, facile route to heterocyclo[b]-fused carbazoles has been developed, simply starting from 1-methylindole. One obvious attractive feature of this synthetic approach is that by appropriate choice of the heteroaryl aldehydes a wide variety of heterocyclo[b]-fused carbazoles can be readily accessible. In this work, five heterocyclo[b]-fused carbazoles **6.7a-e** have been synthesized. Among which **6.7a-d** are the first examples of thieno[3,2-b]carbazole, furo[3,2-b]carbazole, thieno[2,3-b]carbazole and furo[2,3-b]carbazole ring systems prepared.



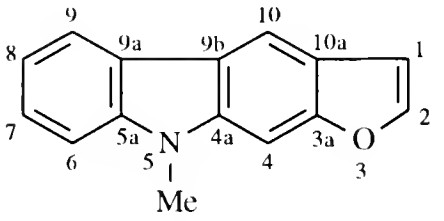
6.7a



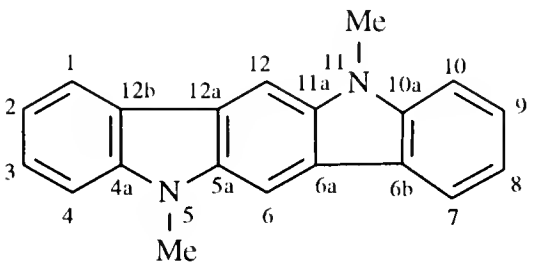
6.7b



6.7c



6.7d



6.7e

Scheme 6.3

6.3 Experimental

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as internal

standard for ^{1}H (300 MHz) or solvent as internal standard for ^{13}C (75 MHz). Assignments for ^{13}C NMR spectra in necessary cases were confirmed by APT experiments. Tetrahydrofuran was distilled under nitrogen immediately before use from sodium / benzophenone. All reactions with air-sensitive compounds were carried out in argon atmospheres. Column chromatography was conducted with silica gel grade 230-400 mesh. 1-Hydroxymethylbenzotriazole and compound **5.2** were prepared according to previous procedure (see Chapter V).

6.3.1 1-Methyl-2-bromo-3-[(benzotriazol-1-yl)methyl]indole(**6.1**):

To a solution of 1-methyl-3-[(benzotriazol-1-yl)methyl]indole (**5.2**) (8.2 mmol, 2.1 g) in methylene chloride (100 ml) was added dropwise a solution of bromine (8.2 mmol, 1.3 g) in methylene chloride (30 ml) at 0°C. After addition was finished, the reaction mixture was further stirred at 0°C for 45 min. Cold sodium bicarbonate solution (5%, 70 ml) was added. The organic layer was further washed with sodium bicarbonate solution (5%, 70 ml), then water. After drying over $MgSO_4$, the solvent was evaporated. The crude product was purified by washing with hot ethyl acetate (20 ml) to give the pure compound in 80% yield. mp 145-146 °C; ^{1}H NMR δ 3.71 (s, 3H, CH_3), 5.96 (s, 2H, CH_2), 7.04-7.07 (m, 1H, In), 7.15-7.27 (m, 3H, Bt and In, overlapped), 7.30-7.35 (m, 1H, Bt), 7.52 (d, J = 8.0 Hz, 1H, In), 7.63 (d, J = 8.0 Hz, Bt), 7.97 (d, J = 8.0 Hz, Bt); ^{13}C NMR δ 31.5 (CH_3), 44.3 (CH_2), 107.9 (In), 109.4 (Bt), 110.0 (In), 115.0 (In), 118.5 (In), 119.7 (In), 120.6 (Bt), 122.5 (In), 123.6 (Bt), 126.2 (In), 127.0 (Bt), 132.4 (Bt), 136.8 (In), 146.1 (Bt). Anal. Calcd for $C_{16}H_{13}N_4Br$: C, 56.32; H, 3.84; N, 16.42. Found: C, 56.46; H, 3.86; N, 16.48.

6.3.2 1-Methyl-2-[(1-hydroxy-1-thien-3-yl)methyl]-3-[(benzotriazol-1-yl)methyl]-indole **6.3**:

To a solution of 1-methyl-2-bromo-3-[(benzotriazol-1-yl)methyl]indole (**6.1**) (3.5 mmol, 1.2 g) in THF (40 ml) was added *tert*-BuLi (4.2 mmol, 2.5 ml, 1.7 M in petane) at -78°C under argon. After 5 min, thiophene-3-carboxaldehyde (4.2 mmol, 0.47 g) in THF (8 ml) was added dropwise. The reaction mixture was stirred at -78°C for 2 h and quenched with water. The organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue subjected to column chromatography (hexanes : ethyl acetate = 3 : 1) to afford pure product (91%). mp 78-79°C; ^{1}H NMR δ 3.34 (s, 3H, NCH_3), 5.32 (d, J = 4.7 Hz, 1H, CH), 5.63 (d, J = 15.4 Hz, 1H, CHBt), 5.70 (d, J = 15.4 Hz, 1H, CHBt), 6.38 (d, J = 3.6 Hz, 1H, thiophene), 6.60 (d, J = 4.7 Hz, 1H, OH), 6.87-7.08 (m, 7H, Bt, In, and thiophene), 7.29 (d, J = 8.2 Hz, 1H, Bt), 7.42 (d, J = 7.9 Hz, 1H, In), 7.60 (d, J = 8.2 Hz, 1H, Bt); ^{13}C NMR δ 30.5 (NCH_3), 42.3 (CH_2), 64.8 (CH), 105.9 (In), 109.3 (In), 109.9 (Bt), 118.2 (In), 119.2 (In), 119.9 (Bt), 121.2 (thiophene), 122.2 (In), 123.7 (Bt), 126.0 (2C, thiophene), 126.4 (In), 127.0 (Bt), 132.4 (Bt), 137.0 (In), 139.2 (In), 142.8 (thiophene), 145.4 (Bt); Anal. Calcd for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96. Found: C, 67.68; H, 4.94; N, 14.93.

6.3.3 General Procedure for the Preparation of Intermediate Products **6.4a-e**:

To the solution of 1-methyl-2-bromo-3-[(benzotriazol-1-yl)methyl]indole (**6.1**) (3.5 mmol, 1.2 g) in THF (40 ml) was added *tert*-BuLi (4.2 mmol, 2.5 ml, 1.7 M in petane) at -78°C under argon. After 5 min, the appropriate aldehyde (4.2 mmol) in THF (8 ml) was added dropwise. The reaction mixture was stirred at -78°C for 2 h.

Methyl iodide (1.7 ml) and HMPA (30 ml) were then added. The mixture was allowed to warm to room temperature and stirred overnight. After aqueous work-up, the crude product was subjected to column chromatography (hexanes : ethyl acetate = 3 : 1) to give pure compound.

1-Methyl-2-[(1-methoxy-1-thien-3-yl)methyl]-3-[(benzotriazol-1-yl)methyl]-indole **6.4a**: ^{1}H NMR δ 3.18 (s, 3H, NCH_3), 3.54 (s, 3H, OCH_3), 5.98 (s, 1H, CH), 6.05 (d, J = 15.5 Hz, 1H, CHBt), 6.14 (d, J = 15.5 Hz, 1H, CHBt), 6.69 (d, J = 5.0 Hz, 1H, thiophene), 6.90 (d, J = 4.3 Hz, 1H, thiophene), 7.14-7.36 (m, 7H, Bt, In, and thiophene, overlapped), 7.76 (d, J = 7.7 Hz, In, 1H), 7.94-7.98 (m, Bt, 1H); ^{13}C NMR δ 30.7 (NCH_3), 42.6 (CH_2), 56.5 (OCH_3), 73.9 (CH), 107.9 (In), 109.4 (In), 109.9 (Bt), 118.3 (In), 119.7 (In), 120.3 (Bt), 121.5 (thiophene), 122.5 (In), 123.6 (Bt), 125.9 (thiophene), 126.0 (thiophene), 126.5 (In), 127.0 (Bt), 132.4 (Bt), 136.2 (In), 137.3 (In), 140.7 (thiophene), 146.1 (Bt).

1-Methyl-2-[(1-methoxy-1-furan-3-yl)methyl]-3-[(benzotriazol-1-yl)methyl]-indole **6.4b**: ^{1}H NMR δ 3.61 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 5.91 (d, J = 2.2 Hz, 1H, furan), 6.03 (s, 1H, CH), 6.04 (d, J = 15.4 Hz, 1H, CHBt), 6.11 (d, J = 15.4 Hz, 1H, CHBt), 7.06 (d, J = 2.2 Hz, 1H, furan), 7.18-7.29 (m, 6H, Bt, In, and furan), 7.36-7.39 (m, 1H, Bt), 7.76 (d, J = 7.0 Hz, 1H, In), 7.94-7.98 (m, 1H, Bt); ^{13}C NMR δ 30.7 (NCH_3), 42.5 (CH_2), 56.3 (OCH_3), 70.8 (CH), 107.7 (In), 108.9 (furan), 109.4 (In), 109.9 (Bt), 118.2 (In), 119.6 (In), 120.2 (Bt), 122.5 (In), 123.5 (Bt), 124.9 (furan), 126.5 (In), 126.9 (Bt), 132.4 (Bt), 135.7 (In), 137.3 (In), 139.5 (furan), 143.2 (furan), 146.0 (Bt).

1-Methyl-2-[(1-methoxy-1-thien-2-yl)methyl]-3-[(benzotriazol-1-yl)methyl]-indole **6.4c**: ^{1}H NMR δ 3.18 (s, 3H, NCH_3), 3.58 (s, 3H, OCH_3), 6.04 (d, J = 14.2 Hz, 1H, CHBt), 6.12 (d, J = 14.2 Hz, 1H, CHBt), 6.14 (s, 1H, CH), 6.40 (d, J = 2.5 Hz,

1H, thiophene), 6.76 (m, 1H, thiophene), 7.15-7.37 (m, 7H), 7.74 (d, J = 7.6 Hz, 1H, In), 7.93-7.96 (m, 1H, Bt); ^{13}C NMR δ 30.9 (NCH_3), 42.5 (CH_2), 56.6 (OCH_3), 73.7 (CH), 108.2 (In), 109.4 (In), 109.9 (Bt), 118.4 (In), 119.6 (In), 120.3 (Bt), 122.6 (In), 123.5 (Bt), 124.4 (thiophene), 125.5 (thiophene), 126.4 (thiophene), 126.5 (In), 126.8 (Bt), 132.4 (Bt), 135.5 (In), 137.3 (In), 143.1 (thiophene), 146.0(Bt).

1-Methyl-2-[(1-methoxy-1-furan-2-yl)methyl]-3-[(benzotriazol-1-yl)methyl]-indole **6.4d**: ^{1}H NMR δ 3.26 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 5.96 (s, 1H, CH), 6.01-6.06 (m, 2H, CHBt and thiophene, overlapped), 6.14 (d, J = 15.5 Hz, 1H, CHBt), 6.21-6.23 (m, 1H, thiophene), 7.14-7.31 (m, 7H, Bt, In, and thiophene, overlapped), 7.67 (d, J = 7.9 Hz, 1H, In), 7.95 (dd, J = 6.9 and 2.9 Hz, 1H, Bt); ^{13}C NMR δ 30.9 (NCH_3), 42.8 (CH_2), 56.7 (OCH_3), 71.6 (CH), 107.6 (In), 108.4 (furan), 109.4 (In), 110.0 (furan), 110.1 (Bt), 118.4 (In), 119.4 (In), 120.2 (Bt), 122.5 (In), 123.4 (Bt), 126.5 (In), 126.7 (Bt), 132.4 (Bt), 134.0 (In), 137.2 (In), 142.6 (furan), 146.0 (Bt), 151.2 (furan).

1-Methyl-2-{[1-methoxy-1-(1-methylindol-3-yl)]methyl}-3-[(benzotriazol-1-yl)methyl]indole **6.4e**: ^{1}H NMR δ 3.23 (s, 3H, NCH_3), 3.41 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 5.99 (d, J = 15.2 Hz, 1H, CHBt), 6.14 (d, J = 15.2 Hz, 1H, CHBt), 6.15 (s, 1H, CH), 6.26 (s, 1H, In), 6.98-7.02 (m, 2H, In), 7.07-7.23 (m, 7H, Bt and In, overlapped), 7.43 (d, J = 8.1 Hz, 1H, Bt), 7.72 (d, J = 7.7 Hz, 1H, In), 7.83 (d, J = 8.1 Hz, 1H, Bt); ^{13}C NMR δ 31.0 (NCH_3), 32.5 (NCH_3), 42.9 (CH_2), 56.5 (OCH_3), 72.6 (CH), 107.4 (In), 109.3 (In), 109.4 (In), 110.3 (Bt), 113.4 (In), 118.8 (In), 119.5 (In), 119.6 (In), 119.7 (In), 120.3 (Bt), 122.0 (In), 122.3 (In), 123.4 (Bt), 126.5 (In, 2C), 127.0 (In), 127.5 (Bt), 132.6 (Bt), 136.7 (In), 137.3 (In, 2C), 146.0 (Bt).

6.3.4 General Procedure for the Preparation of Heterocyclo[b]-fused Carbazoles **6.7a-e**:

A solution of the corresponding intermediate products **6.4** (1.6 mmol) in 1,2,4-trichlorobenzene (40 ml) (for **6.4a-d**) or in 1,2-dichlorobenzene (40 ml) (for **6.4e**) was refluxed under argon for 48 h. The solvent was evaporated and the residue was subjected to column chromatography (hexanes : methylene chloride = 4 : 1) to give pure product.

5-Methylthieno[3,2-b]carbazole **6.7a**: ^{1}H NMR δ 3.80 (s, 3H, CH_3), 7.18-7.23 (t, J = 7.7 Hz, 1H, 8-H), 7.38-7.51 (m, 4H), 7.72 (s, 1H, 4-H), 8.08 (d, J = 7.7 Hz, 1H, 9-H), 8.48 (s, 1H, 10-H); ^{13}C NMR δ 28.2 (CH_3), 100.8, 107.3, 112.4, 117.8, 119.3, 120.8, 121.5, 122.7, 125.4, 125.8, 130.4, 137.4, 139.1, 141.3.

5-Methylfuro[3,2-b]carbazole **6.7b**: ^{1}H NMR δ 3.79 (s, 3H, NCH_3), 7.86 (d, J = 2.2 Hz, 1H, 3-H), 7.21 (t, J = 7.7 Hz, 1H, 8-H), 7.33 (d, J = 7.7 Hz, 1H, 6-H), 7.42 (s, 1H, 4-H), 7.47 (t, J = 7.7 Hz, 1H, 7-H), 7.69 (d, J = 2.2 Hz, 1H, 2-H), 8.10 (d, J = 7.7 Hz, 1H, 9-H), 8.15 (s, 1H, 10-H); ^{13}C NMR δ 29.2 (NCH_3), 98.4, 101.8, 106.7, 108.1, 118.3, 120.1, 121.4, 122.8, 125.8, 126.7, 138.8, 142.1, 145.7, 150.2.

5-Methylthieno[2,3-b]carbazole **6.7c**: ^{1}H NMR δ 3.79 (s, 3H, CH_3), 7.21-7.37 (m, 3H), 7.43 (d, J = 5.5 Hz, 1H, 2-H), 7.49 (t, J = 7.5 Hz, 1H, 7-H), 7.76 (s, 1H, 4-H), 8.13 (d, J = 7.5 Hz, 1H, 9-H), 8.45 (s, 1H, 10-H); ^{13}C NMR δ 29.2 (CH_3), 100.7, 108.2, 114.4, 118.7, 120.3, 122.5, 122.8, 122.9, 123.8, 126.1, 133.0, 138.6, 140.3, 142.2.

5-Methylfuro[2,3-b]carbazole **6.7d**: ^{1}H NMR δ 3.82 (s, 3H, CH_3), 6.88 (d, J = 2.3 Hz, 1H, 1-H), 7.22-7.25 (m, 1H, 6-H), 7.35-7.46 (m, 3H), 7.62 (d, J = 2.3 Hz, 1H, 2-H), 8.11 (d, J = 8.0 Hz, 1H, 9-H), 8.21 (s, 1H, 10-H); ^{13}C NMR δ 29.3 (CH_3), 90.6,

106.7, 108.1, 111.5, 118.7, 119.9, 120.5, 120.9, 122.9, 125.3, 141.9, 143.9, 148.4, 154.8.

5,11-Dimethylindolo[3,2-b]carbazole **6.7e**: ^{1}H NMR δ 3.87 (s, 6H, $2CH_3$), 7.14-7.19 (m, 2H, H-2,8), 7.33 (d, J = 8.0 Hz, 2H, H-4,10), 7.40-7.43 (m, 2H, H-3,9), 7.93 (s, 2H, H-6,12), 8.12 (d, J = 7.8 Hz, 2H, H-1,7); ^{13}C NMR δ 29.4 ($2CH_3$), 98.6 (C-4, C-10), 108.1 (C-1, C-7), 118.1 (C-3, C-9), 120.1 (C-2, C-8), 122.8 (C-6b, C-12b), 122.9 (C-6a, C12a), 125.7 (C-6, C-12), 136.8 (C-4a, C-10a), 142.2 (C-5a, C-11a).

Table 6.1 Preparation of Intermediate Products **6.4a-e**

Compd	Yield (%)	Het	mp(°C)	Molecular Formula	found			required		
					C	H	N	C	H	N
6.4a	81	thien-3-yl	117-118	$C_{22}H_{20}N_4OS$	67.69	5.14	14.48	68.02	5.19	14.42
6.4b	86	furan-3-yl	79-80	$C_{22}H_{20}N_4O_2$	70.59	5.08	15.15	70.94	5.42	15.05
6.4c	88	thien-2-yl	54-55	$C_{22}H_{20}N_4OS$	68.39	5.29	14.21	68.02	5.19	14.42
6.4d	84	furan-2-yl	oil	$C_{22}H_{20}N_4O_2$	70.61	5.11	15.29	70.94	5.42	15.05
6.4e	88	indol-3-yl	98-99	$C_{27}H_{25}N_5O$	74.35	5.78	15.70	74.46	5.79	16.08

Table 6.2 Preparation of Heterocyclo[b]-fused Carbazoles **6.7a-e**

Compd	Yield (%)	mp(°C)	Molecular Formula	found			required		
				C	H	N	C	H	N
6.7a	55	168-169	$C_{15}H_{11}NS$	75.79	4.70	5.84	75.92	4.67	5.90
6.7b	67	121-122	$C_{15}H_{11}NO$	81.36	5.00	6.25	81.42	5.01	6.33
6.7c	56	177-178	$C_{15}H_{11}NS$	76.06	4.66	5.83	75.92	4.67	5.90
6.7d	43	116-117	$C_{15}H_{11}NO$	81.74	5.10	6.30	81.42	5.01	6.33
6.7e	31	287-288 *	$C_{20}H_{16}N_2$	84.84	5.86	9.66	84.48	5.67	9.85

* Lit. mp. 295-296 [76LA1090]

CHAPTER VII
CONCLUSION

A wide spectrum of useful organic compounds, α-functionalized isonitriles, substituted benzyl phenyl sulfides, both symmetrical and unsymmetrical 1,1-bis(heteroaryl)alkanes, 3-substituted indoles and heterocyclo[b]-fused carbazoles, have been synthesized *via* benzotriazole mediated heteroalkylation and arylalkylation methodology.

The ease with which various types of benzotriazole derivatives can be prepared and the benzotriazolyl group can be displaced subsequently by a wide range of nucleophiles proves this methodology to be general and facile.

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Some commonly used additional notes are given below:

1. The list of reference is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
2. In the reference list the code is followed by the complete literature citation in the conventional manner.
3. For journals which are published in separate parts, the part letter of number is given (when necessary) in parentheses immediately after the journal code letters.
4. Journal volumn numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the

volume number is included in parentheses immediately after the journal code letters.

5. Patents are assigned appropriate three letter codes.

6. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter "B-".

7. Less common journals and books are given the code "MI" for miscellaneous.

8. Where journals have changed names, the same code is used throughout.

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BIOGRAPHICAL SKETCH

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She is married to Jianqing Li who is doing his Ph.D. also under the supervision of Professor Katritzky. She has a one-year-old daughter, Stephanie, who was born in Gainesville.

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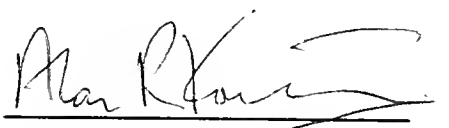

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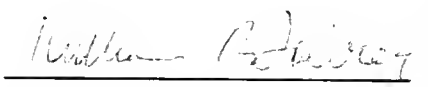

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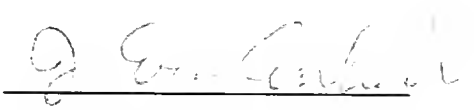

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December, 1994

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